

Table 5-34 (Continued): Epidemiologic studies of PM_{10-2.5} and respiratory related hospital admissions and emergency department (ED) visits.

Study, Location, Years, Age Range	Exposure Assessment/Measurement of PM _{10-2.5} Concentrations	ICD Codes ICD-9 or ICD-10	Mean Concentration µg/m ³	Upper Percentile Concentrations µg/m ³	Copollutant Examination
ED visits					
<u>Peel et al. (2005)</u> Atlanta, GA 1993–2000 All ages	One monitor Direct measurement of PM _{10-2.5} concentration by a dichotomous monitor (<u>Van Loy et al., 2000</u>).	460–466, 477; 480–486; 491, 492, 496; 493, 786.09	19.2	90th: 32.3	Correlation (r): 0.55–0.68, CO, NO ₂ Copollutant models with: NA
<u>Tolbert et al. (2007)</u> Atlanta, GA 1993–2004 All ages	One monitor Direct measurement of PM _{10-2.5} concentration by a dichotomous monitor (<u>Van Loy et al., 2000</u>).	460–465, 460.0, 477; 480–486; 491, 492, 496; 493, 786.07, 786.09; 466.1, 466.11, 466.19	17.1	75th: 21.9 90th: 28.8 Max: 65.8	Correlation (r): 0.62 O ₃ , 0.47 NO ₂ , 0.47 CO, 0.17 SO ₂ , 0.47 PM _{10-2.5} Copollutant models with: NA
<u>†Malig et al. (2013)</u> 35 California counties 2005–2008 All ages	Difference of collocated PM ₁₀ and PM _{2.5} concentrations, assigned from the nearest monitoring station within 20 km of population-weighted zip code centroid.	460–519	5.6–34.4	NR	Correlation (r): 0.31 PM _{2.5} , 0.38 O ₃ , 0.14 CO Copollutant models with: PM _{2.5} , O ₃ , NO ₂ , CO, SO ₂

Table 5-34 (Continued): Epidemiologic studies of PM_{10-2.5} and respiratory related hospital admissions and emergency department (ED) visits.

Study, Location, Years, Age Range	Exposure Assessment/Measurement of PM _{10-2.5} Concentrations	ICD Codes ICD-9 or ICD-10	Mean Concentration µg/m ³	Upper Percentile Concentrations µg/m ³	Copollutant Examination
Hospital admissions and ED visits, separately					
†Rodopoulou et al. (2014) Doña Ana County, NM 2007–2010 ≥18 yr	Three monitors PM _{10-2.5} concentration estimated by calculating difference between PM ₁₀ and PM _{2.5} concentrations; not clearly stated if PM _{10-2.5} concentrations were averaged across monitors, if assignment came from the nearest monitor, or if PM ₁₀ and PM _{2.5} monitors were collocated.	460–465, 466, 480–486, 490–493, 496	10.9	75th: 13 Max: 55.6	Correlation (r): –0.05 O ₃ Copollutant models with: NA

CMAQ = Community Multi-Scale Air Quality model; MED-PARTICLES = particles size and composition in Mediterranean countries: geographical variability and short-term health effects; UFIREF = ultrafine particles—an evidence-based contribution to the development of regional and European environmental and health policy.

^aMedian concentration

^bOnly four of the five cities had PM_{10-2.5} data.

^cOnly six of the eight cities had PM_{10-2.5} data.

†Studies published since the 2009 PM ISA.

Recent multicity studies ([Lanzinger et al., 2016b](#); [Samoli et al., 2016a](#); [Powell et al., 2015](#); [Stafoggia et al., 2013](#)) and single-city studies ([Rodopoulou et al., 2014](#); [Alessandrini et al., 2013](#); [Atkinson et al., 2010](#)) conducted in the U.S. and Europe that examined the association between short-term PM_{10-2.5} exposure and respiratory-related hospital admissions provide evidence of positive associations that vary in terms of magnitude and precision ([Figure 5-44](#)), particularly in analyses of people of all ages. In a limited assessment of potential copollutant confounding, associations were often attenuated, but remained positive in copollutant models with PM_{2.5}, NO₂, and O₃ ([Powell et al., 2015](#); [Alessandrini et al., 2013](#); [Stafoggia et al., 2013](#)). The positive associations reported across these studies is supported by a meta-analysis focusing on PM_{10-2.5} and respiratory hospital admissions that reported a RR = 1.01 (95% CI: 1.00, 1.02) ([Adar et al., 2014](#)). Additional analyses conducted by [Adar et al. \(2014\)](#) to assess potential copollutant confounding by PM_{2.5} did not observe a consistent pattern in PM_{10-2.5} associations as the correlation with PM_{2.5} increased or when evaluating studies that examined associations with both PM_{2.5} and PM_{10-2.5}.

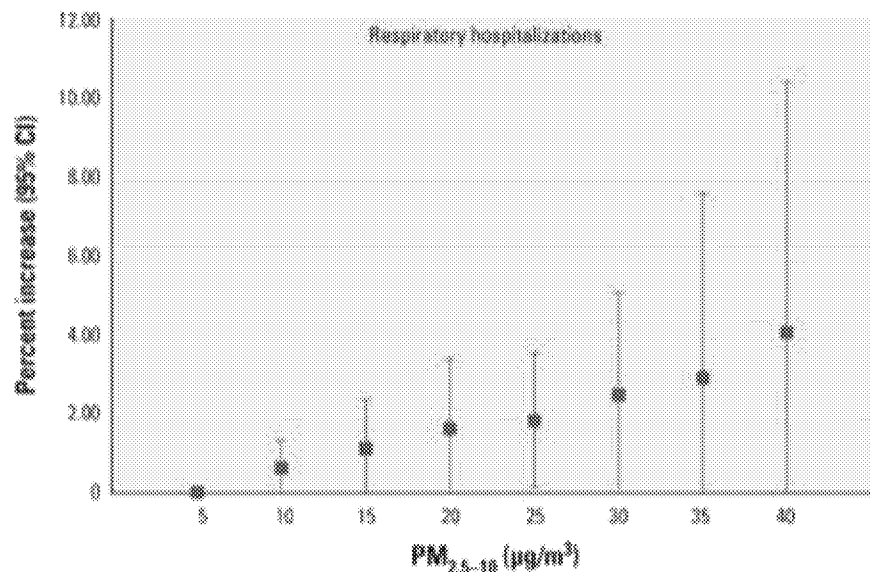
Additional single-city studies conducted in London, U.K. ([Atkinson et al., 2010](#)) and Rome, Italy, ([Alessandrini et al., 2013](#)) also contribute to the total body of evidence for respiratory-related hospital admissions. [Atkinson et al. \(2010\)](#) when examining a number of urban particles, examined associations with PM_{10-2.5} and across single-day lags ranging from 0 to 6 days. The authors reported evidence of a positive association at lag 1 in an all ages analysis, but there was no evidence of an association for the other lags examined (quantitative results not presented). Instead of focusing on urban particles, [Alessandrini et al. \(2013\)](#) examined the role of Saharan dust on the relationship between short-term PM_{10-2.5} exposure and respiratory-related hospital admissions. Across the entire study duration, the authors reported a 4.4% increase (95% CI: -0.53, 9.60) in hospital admissions at lag 0–5 days. However, when differentiating between Saharan and non-Saharan dust days, [Alessandrini et al. \(2013\)](#) observed that the overall association reported was primarily attributed to the Saharan dust days (13.5%) compared to the non-Saharan dust days (-0.30%).

Across the hospital admissions studies evaluated, a few of the studies conducted sensitivity analyses to examine the lag structure of associations and model specification. Both [Stafoggia et al. \(2013\)](#) and [Lanzinger et al. \(2016b\)](#) examined whether there is evidence of immediate (lag 0–1), delayed (lag 2–5), or prolonged (lag 0–5) effects of PM_{10-2.5} on respiratory-related hospital admissions. In both studies, positive associations were observed across each of the lags, with the association largest in magnitude at lag 0–5, indicating a potential prolonged effect [([Stafoggia et al., 2013](#)): lag 0–1, 1.0% [95% CI: 0.10, 1.8]; lag 2–5: 1.2% [95% CI: -1.1, 3.6]; lag 0–5: 2.0% [95% CI: -0.51, 4.5]; ([Lanzinger et al., 2016b](#)): lag 0–1, 7.4% [95% CI: 1.9, 12.7]; lag 2–5: 10.7% [95% CI: 4.7, 16.9]; lag 0–5: 13.9% [95% CI: 6.9, 21.3]]. However, in [Stafoggia et al. \(2013\)](#), as the lag days increased, the confidence intervals did as well, resulting in more uncertain estimates. The results of [Stafoggia et al. \(2013\)](#) and [Lanzinger et al. \(2016b\)](#) are supported by [Samoli et al. \(2016a\)](#) when examining single-day lags ranging from 0 to 10 days where positive associations were observed through lag Day 4, but the strongest

1 association in terms of magnitude and precision was a lag 1 (quantitative results not presented). Stafoggia
2 et al. (2013) and Powell et al. (2015) both examined the influence of alternative approaches to account for
3 temporal trends and the confounding effects of weather and found that results were relatively unchanged.

4 Similar to the 2009 PM ISA (U.S. EPA, 2009), compared to studies that examined short-term
5 $PM_{10-2.5}$ exposure and respiratory-related hospital admissions, fewer studies focused on ED visits with the
6 evidence primarily limited to single-city studies. In analyses of all ages, there is no evidence of an
7 association when examining the results from single-city studies. Rodopoulou et al. (2014) in a study
8 conducted in Doña Ana County, NM reported a positive association for older adults, but no evidence of
9 an association for an all ages analysis, which is consistent with the single-city studies evaluated in the
10 2009 PM ISA (Figure 5-44). However, Malig et al. (2013), in a study of 35 California counties, reported
11 positive associations at lags 1 and 2 days, with the strongest association in terms of magnitude and
12 precision at lag 1 (0.7% [95% CI: 0.3, 1.1]). The association with $PM_{10-2.5}$ was found to remain positive in
13 copollutant models with O_3 , NO_2 , CO , SO_2 , and $PM_{2.5}$. Additionally, associations were found to be
14 slightly elevated in the warm compared to cold season, and robust to the exclusion of extreme $PM_{10-2.5}$
15 values (the highest and lowest 5% of calculated coarse particle levels) from the analysis. Rodopoulou et
16 al. (2014) also examined the influence of season and extreme $PM_{10-2.5}$ concentrations and reported
17 contradictory results to Malig et al. (2013), i.e., associations larger in magnitude in the cold season and
18 that the $PM_{10-2.5}$ association increased in magnitude when excluding high $PM_{10-2.5}$ concentrations.
19 Uncertainties in how $PM_{10-2.5}$ concentration was estimated in Rodopoulou et al. (2014) complicates the
20 comparison between studies.

21 Recent studies of respiratory-related hospital admissions and ED visits provide an initial
22 assessment of the C-R relationship, but is limited by the studies not conducting extensive empirical
23 evaluations of alternatives to linearity, and whether there is evidence of a threshold below which effects
24 are not observed. Malig et al. (2013) provides initial evidence of a log-linear relationship through an
25 analysis where the inclusion of a squared term for $PM_{10-2.5}$ into the statistical model to account for
26 possible nonlinearity did not improve the goodness of fit over the initial model that assumed linearity.
27 Stafoggia et al. (2013) examined whether there was evidence of a threshold in a study of six European
28 cities, which is similar the threshold analysis detailed for $PM_{2.5}$ (Section 5.1.10.6). As depicted in Table 5-
29 45, the authors examined the percent increase in hospital admissions at various concentrations across the
30 distribution of $PM_{10-2.5}$ concentrations, up to $40 \mu g/m^3$, relative to $5 \mu g/m^3$, and reported no evidence a
31 threshold.



Source: Permission pending, Adapted from Stafoggia et al. (2013).

Figure 5-45 Concentration-response relationship between short-term PM_{10-2.5} exposure and respiratory-related hospital admissions, lag 0–5, relative to 5 µg/m³.

5.3.6 Respiratory Effects in Healthy Populations

The 2009 PM ISA (U.S. EPA, 2009) evaluated a limited number of studies that examined the effects of short-term exposure to PM_{10-2.5} on respiratory effects in healthy populations. No epidemiologic studies were available on PM_{10-2.5} exposure and respiratory effects in healthy populations. Null findings were reported for lung function in populations of children, but their health status was not reported (Dales et al., 2008; Moshhammer et al., 2006). Evidence for inflammation was inconsistent in controlled human exposure studies. Alexis et al. (2006) found evidence of pulmonary inflammation, as well as innate immune responses of airway macrophages, and increased levels of eotaxin in healthy individuals. Some of these responses were reduced by biological inactivation (i.e., heat-treatment of PM_{10-2.5}) implicating a role for endotoxin. Additionally, short-term exposure to PM_{10-2.5} particles was also shown to elicit increases in polymorphonuclear leukocytes and inflammatory cytokines in healthy adults (Graff et al., 2009). However, Jr et al. (2004) reported no effect of short-term PM_{10-2.5} exposure on markers of airway inflammation in healthy subjects. Animal toxicological studies employed noninhalation routes of exposure since inhalation exposure of rodents to PM_{10-2.5} is technically difficult given that rodents are obligatory nasal breathers. A number of studies of involving noninhalation routes of exposure (i.e., oropharyngeal aspiration, intra-tracheal instillation) support a potential role of short-term PM_{10-2.5} exposure in pulmonary oxidative stress and inflammation (Gilmour et al., 2007; Happonen et al., 2007; Dick et al., 2003). Evidence for pulmonary injury, oxidative stress, inflammation, and morphological changes

was also provided by [Gerlofs-Nijland et al. \(2007\)](#); [Gerlofs-Nijland et al. \(2005\)](#) in studies involving intra-tracheal instillation of PM_{10-2.5} and an animal model of cardiovascular disease.

5.3.6.1 Epidemiologic Studies

Recent studies have used scripted exposures of healthy adults alternating between rest and exercise in high- and low-pollution locations. These studies minimize uncertainty in the PM_{10-2.5} exposure metric by measuring personal ambient PM_{10-2.5} at the site of exposure (calculated as the difference between PM₁₀ and PM_{2.5}). In Utrecht, the Netherlands, PM_{10-2.5} exposure of 5 hours was associated with a decrease in FVC and an increase in eNO ([Strak et al., 2012](#)). However, the observed associations were small in magnitude and the authors did not report confidence intervals or other measures of precision. Two-hour PM_{10-2.5} exposure was also associated with increased eNO, but not with any of the number of lung function metrics measured in a study of healthy adults in Barcelona, Spain ([Kubesch et al., 2015](#)). In a follow-up study using a similar design, [Matt et al. \(2016\)](#) reported FEV₁, FVC, and PEF decrements associated with PM_{10-2.5}. Results appeared to be transient, as associations were observed immediately after exposure, but not 7 hours later during a follow-up spirometry test ([Matt et al., 2016](#)). Inconsistent associations among the vast number of pollutants and outcomes analyzed within studies is a limitation of all the reviewed studies.

There is limited evidence in healthy children in Chile, Sweden, and Taiwan for associations with 24-hour average PM_{10-2.5} concentrations (difference between PM₁₀ and PM_{2.5} measured at monitors). Repeated measures of respiratory symptoms and eNO were associated with PM_{10-2.5} concentrations at a monitor within 1.5 or 3 km of home or school ([Prieto-Parra et al., 2017](#); [Carlsen et al., 2016](#)). In a cross-sectional analysis, PM_{10-2.5} averaged across city monitors were associated with decreases in FEV₁, FVC, MMEF, FEV₁/FVC, and MMEF/FVC ([Chen et al., 2015a](#)). Cross-sectional measurements are generally less informative than repeated measures study designs because they do not establish a temporal relationship between the exposure and outcome of interest. Other findings in children are inconsistent, but do not provide insight into the respiratory effects of PM_{10-2.5} exposure in healthy people because they are for a population with 66% prevalence of asthma or allergy ([Chen et al., 2012](#); [Chen et al., 2011a](#)) or infants on cardiorespiratory monitors who may not spend much time outdoors away from home ([Peel et al., 2011](#)).

5.3.6.2 Controlled Human Exposure

In a recent study, [Behbod et al. \(2013\)](#) exposed subjects to PM_{10-2.5} CAPs and measured multiple markers of airway inflammation, but relative to filtered air, no significant airway (sputum) responses were found (Table 5-35).

Table 5-35 Study-specific details from a controlled human exposure study of short-term PM_{10-2.5} exposure and respiratory effects in a healthy population.

Study	Study Design	Disease Status; n; Sex; (Age)	Exposure Details (Concentration; Duration; Comparison Group)	Endpoints Measured
Behbod et al. (2013)	Double-blind, randomized cross-over block design	Healthy nonsmokers; n = 35; 11 M, 12 F (18–60 yr)	234.7 µg/m ³ PM _{2.5} (IQR: 52.4 µg/m ³) for 130 min (120-min exposure + 10 min to complete tests) at rest. Comparison groups were either (1) filtered air or (2) medical air; a minimum 2-week washout period was used between exposures.	Sputum (pre- and 24-hour post-exposure); Total cell and neutrophil counts

BAL = bronchoalveolar lavage; IL-6 = interleukin-6, IL-8 = interleukin-8, IQR = interquartile range.

5.3.6.3 Animal Toxicological Studies

Recent studies involving intra-tracheal instillation confirm previous results showing that PM_{10-2.5} collected during different seasons and from different locations exhibits variable potency in terms of pulmonary injury, inflammation, and morphologic changes ([Lippmann et al., 2013a](#); [Mirowsky et al., 2013](#); [Halatek et al., 2011](#)). In addition, two recent animal inhalation studies provide evidence for respiratory effects in healthy populations resulting from short-term exposure to PM_{10-2.5}. [Amatullah et al. \(2012\)](#) found that a 4-hour inhalation exposure of BALB/c mice to PM_{10-2.5} CAPs in Toronto increased baseline total respiratory resistance ($p < 0.05$) and maximum response to methacholine ($p < 0.01$) immediately after exposure. In addition, quasi-static compliance was decreased ($p < 0.01$) and quasi-static elastance was increased ($p < 0.01$). These changes indicate airway obstruction. [Amatullah et al. \(2012\)](#) also found increased total cells and macrophages in the bronchoalveolar lavage fluid (BALF) ($p < 0.05$). [Aztatzi-Aguilar et al. \(2015\)](#) showed that multiday inhalation exposure of Sprague Dawley rats to PM_{10-2.5} CAPs in Mexico City resulted in increased IL-6 protein in lung tissue ($p < 0.05$). In addition, a reduction in angiotensin converting enzyme was observed ($p < 0.05$). Angiotensin converting enzyme is a component of the RAS and regulates levels of the potent vasoconstrictor angiotensin II. Since deposition of inhaled PM_{10-2.5} is expected to primarily occur in the extrathoracic airways (i.e., the nose) of rodents, recent animal toxicological studies links deposition in the nose to changes in pulmonary function including increased airway responsiveness, inflammation in the lower airways, and changes in the RAS. Additional study details for these recent toxicological studies are found in Table 5-36.

Table 5-36 Study-specific details from animal toxicological studies of short-term PM_{10-2.5} exposure and respiratory effects in healthy animals.

Study/Study Population	Pollutant	Exposure	Endpoints
<u>Amatullah et al. (2012)</u> Species: Mouse Sex: Female Strain: BALB/c Age/Weight: 6–8 weeks, 18 g	PM _{10-2.5} CAPs Toronto Particle size: PM _{10-2.5} Control: HEPA-filtered air	Route: Nose-only inhalation Dose/Concentration: PM _{10-2.5} 793 µg/m ³ , duration: 4 h Time to analysis: At end of exposure Modifier: Baseline ECG	Pulmonary function—airways resistance, quasi-static elastance BALF cells
<u>Aztatzi-Aguilar et al. (2015)</u> Species: Rat Sex: Male Strain: Sprague Dawley	PM _{10-2.5} CAPs Mexico City Particle size: PM _{10-2.5} Control: Filtered air	Route: Inhalation Dose/Concentration: PM _{10-2.5} 32 µg/m ³ Duration: Acute 5 h/day, 3 days Time to analysis: 24 h	Gene and protein expression in lung tissue <ul style="list-style-type: none"> • IL-6 • Components of RAS and kalikrein-kinin endocrine system • Heme oxygenase-1

BALF = bronchoalveolar lavage fluid; ECG = electrocardiogram; IL-6 = interleukin 6; RAS = renin-angiotensin system.

5.3.6.4 Summary of Respiratory Effects in Healthy Populations

Epidemiologic and controlled human exposure studies examining healthy populations do not consistently support a relationship between PM_{10-2.5} and lung function or pulmonary inflammation. Animal toxicological studies provide evidence for decrements in lung function, inflammation, oxidative stress, and upregulation of the RAS system following short-term inhalation exposure to PM_{10-2.5}. Support for some of these findings in animals are provided by studies using noninhalation routes of exposure.

5.3.7 Respiratory Mortality

Studies that examine the association between short-term PM_{10-2.5} exposure and cause-specific mortality outcomes, such as respiratory mortality, provide additional evidence for PM_{10-2.5}-related respiratory effects, specifically whether there is evidence of an overall continuum of effects. In the 2009 PM ISA (U.S. EPA, 2009), only a few studies examined the association between short-term PM_{10-2.5} exposure and respiratory mortality, with only one U.S. based multicity study (Zanobetti and Schwartz, 2009). Across studies, there was evidence of generally positive associations with respiratory mortality even though studies used a variety of approaches to estimate PM_{10-2.5} concentrations, but confidence intervals were wide in the single-city studies evaluated. Overall, there was limited evaluation of the

potential confounding effects of gaseous pollutants and the influence of model specification on the associations observed.

Recent multicity epidemiologic studies that examined associations between short-term $PM_{10-2.5}$ exposure and respiratory mortality provide evidence of positive associations in some locations, but not in others (Figure 11-27). However, a meta-analysis (Adar et al., 2014) indicates a $PM_{10-2.5}$ association similar in magnitude as the multicity U.S. based study (Zanobetti and Schwartz, 2009) evaluated in the 2009 PM ISA (U.S. EPA, 2009). Unlike the studies evaluated in the 2009 PM ISA, some recent studies have also further evaluated the $PM_{2.5}$ -respiratory mortality relationship by examining cause-specific respiratory mortality outcomes (i.e., COPD, pneumonia, and LRTI) (Samoli et al., 2014; Janssen et al., 2013). Overall, the results reported in the studies that examine cause-specific respiratory mortality outcomes are generally consistent with the results for all respiratory mortality, but the smaller number of mortality events observed results in estimates with larger uncertainty. As a result, this section focuses on studies that examine all respiratory mortality outcomes and address uncertainties and limitations in the relationship between short-term $PM_{10-2.5}$ exposure and respiratory mortality, specifically: potential copollutant confounding, lag structure of associations, and effect modification by season and temperature.

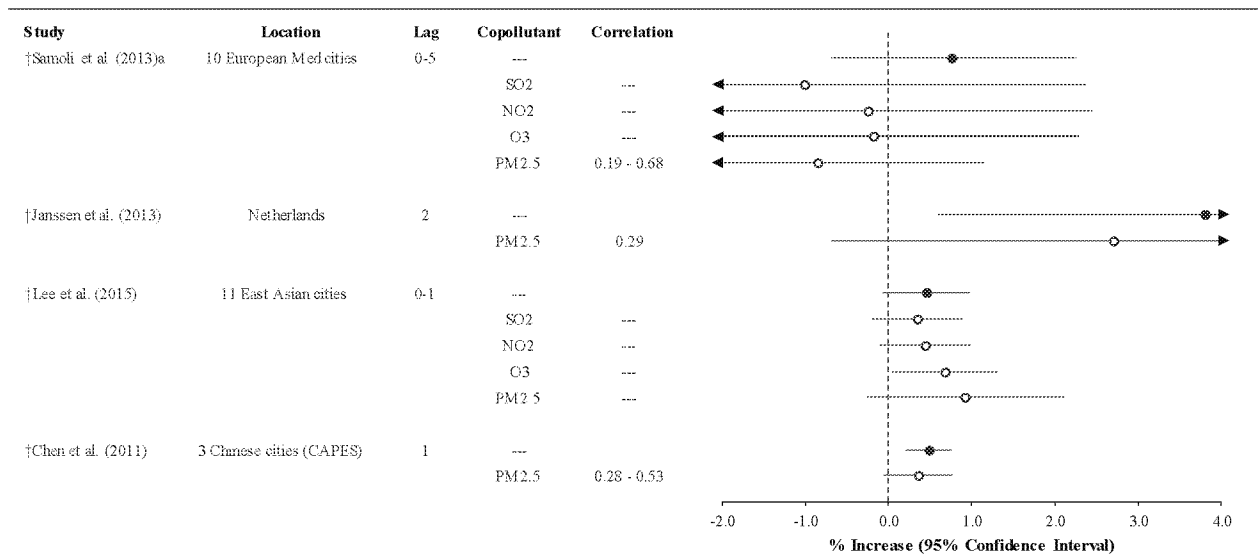
5.3.7.1 Characterizing the $PM_{10-2.5}$ -Respiratory Mortality Relationship

Recent epidemiologic studies conducted additional analyses that address some of the uncertainties and limitations of the relationship between short-term $PM_{10-2.5}$ exposure and respiratory mortality identified in the 2009 PM ISA (U.S. EPA, 2009). Specifically, recent studies provide additional information on copollutant confounding, lag structure of associations, and seasonal associations. However, similar to those studies evaluated in the 2009 PM ISA, the approaches used to estimate $PM_{10-2.5}$ concentrations varies across studies and it remains unclear if the level of exposure measurement error varies by each approach (Table 11-9). Overall, these studies provide initial evidence that: $PM_{10-2.5}$ -respiratory mortality associations remain positive but may be attenuated in copollutant models; $PM_{10-2.5}$ effects on respiratory mortality tend to occur within the first few days of exposure (i.e., lags 0 to 2 days); and it remains unclear if there are seasonal differences in associations.

5.3.7.1.1 Copollutant Confounding

Consistent with the evaluation of total (nonaccidental) mortality, the studies evaluated in the 2009 PM ISA (U.S. EPA, 2009) provided limited information on the potential confounding effects of gaseous pollutants and $PM_{2.5}$ on the relationship between short-term $PM_{10-2.5}$ exposure and respiratory mortality. Recent multicity studies (Lee et al., 2015; Janssen et al., 2013; Samoli et al., 2013; Chen et al., 2011b) and a meta-analysis (Adar et al., 2014) provide additional information concerning the role of copollutants on the $PM_{10-2.5}$ -respiratory mortality relationship.

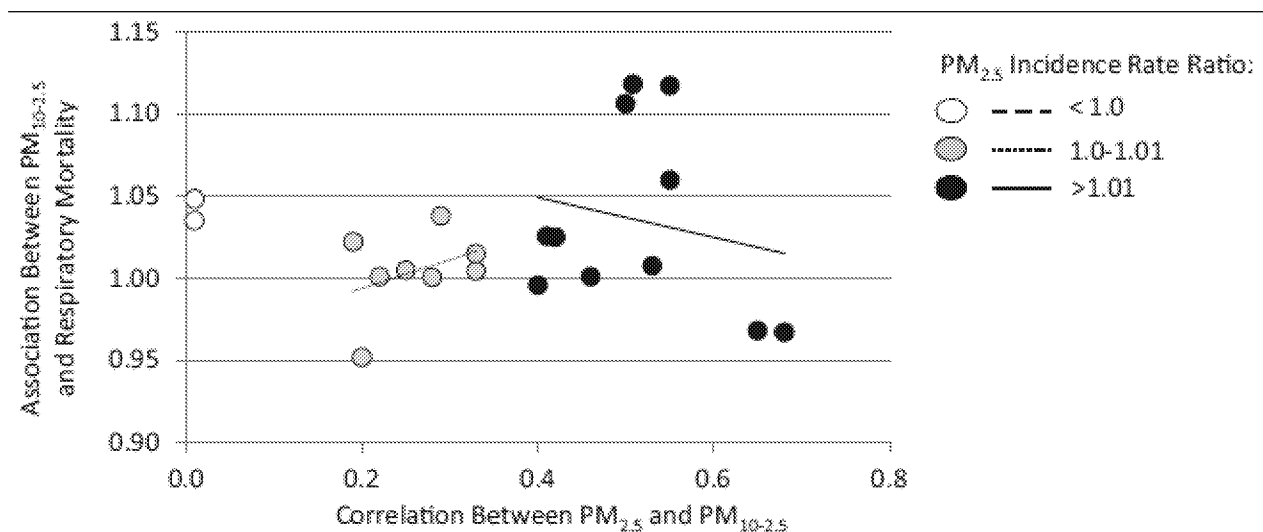
When focusing on potential copollutant confounding of the PM_{10-2.5}-respiratory mortality relationship by PM_{2.5}, there is evidence that the association generally remains positive (Figure 5-46). However, Samoli et al. (2013) in a study of 10 European Mediterranean cities within the MED-PARTICLES project did not find any evidence of PM_{10-2.5}-respiratory mortality association in copollutant models with PM_{2.5}. Unlike the other studies evaluated, the authors only presented copollutant model results for lag 0–5 days, which is a lag structure that is longer and inconsistent with the larger body of evidence (Section 5.3.7.1.2).



Note: †Studies published since the 2009 PM ISA. ^a = copollutant results only presented for a lag of 0–5 days. Corresponding quantitative results are reported in Supplemental Material (U.S. EPA, 2018).

Figure 5-46 Percent increase in respiratory mortality for a 10 µg/m³ increase in 24-hour average PM_{10-2.5} concentrations in single- and copollutant models.

The studies that provide evidence of a $PM_{10-2.5}$ -respiratory mortality association that remains positive in copollutant models with $PM_{2.5}$ are supported by analyses conducted by [Adar et al. \(2014\)](#) in the context of a meta-analysis. When examining studies that conducted copollutant models with $PM_{2.5}$, [Adar et al. \(2014\)](#) observed that the $PM_{10-2.5}$ -respiratory mortality association was similar in magnitude to that observed in single-pollutant models (quantitative results not provided). The results from copollutant models were further supported when stratifying $PM_{10-2.5}$ -mortality estimates by the correlation with $PM_{2.5}$ (low, $r < 0.35$; medium, $r = 0.35$ to <0.5 ; high, $r > 0.5$). The authors observed evidence of positive associations for the medium and high correlation categories that were similar in magnitude, but had wide confidence intervals. However, there was no evidence of an association for the low correlations. [Adar et al. \(2014\)](#) further examined potential copollutant confounding by $PM_{2.5}$ through an analysis focusing on whether $PM_{10-2.5}$ -mortality associations were present when the correlation between $PM_{2.5}$ and $PM_{10-2.5}$ increased and when $PM_{2.5}$ was also associated with mortality. As highlighted in [Figure 5-47](#), there was evidence of positive $PM_{10-2.5}$ -respiratory mortality associations at both low and high correlations as well as low and high magnitudes of the $PM_{2.5}$ -respiratory mortality association ([Figure 5-47](#)).



Source: Permission pending, [Adar et al. \(2014\)](#).

Figure 5-47 Associations between short-term $PM_{10-2.5}$ exposure and respiratory mortality as a function of the correlation between $PM_{10-2.5}$ and $PM_{2.5}$ stratified by strength of the association with $PM_{2.5}$.

Across the studies that examined potential copollutant confounding, only a few examined gaseous pollutants ([Lee et al., 2015](#); [Samoli et al., 2013](#)) and the results contradict one another (see [Figure 5-46](#)).

As a result, it remains unclear whether gaseous copollutants confound the PM_{10-2.5}-respiratory mortality association.

Collectively, the recent epidemiologic studies that examined potential copollutant confounding provide initial evidence that PM_{10-2.5}-respiratory mortality associations remain generally positive in copollutant models particularly with PM_{2.5}. However, the lack of information on the correlations among the pollutants examined and the limited analyses of gaseous pollutants complicates the interpretation of the copollutant model results.

5.3.7.1.2 Lag Structure of Associations

Multicity epidemiologic studies that examined cause-specific mortality in the 2009 PM ISA (U.S. EPA, 2009) observed immediate effects on respiratory mortality attributed to short-term PM_{10-2.5} exposure, with consistent positive associations observed at lags ranging from 0 to 2 days. However, the majority of these studies either examined single-day lags or selected lags a priori. Recent multicity studies have conducted more extensive examinations of the lag structure of associations by examining multiple sequential single-day lags or examining whether there is evidence of immediate (i.e., lag 0–1 days), delayed (i.e., lag 2–5 days), or prolonged (i.e., lag 0–5 days) effects of short-term PM_{10-2.5} exposure on respiratory mortality.

Across the studies that examined single-lag days, most of the studies focused on lags within the range of 0 to 2 days. Although a few studies extended out to a longer duration, collectively the studies provided evidence that was generally in agreement with one another. Janssen et al. (2013), in a study conducted in the Netherlands, examined single-day lags of 0 to 3 days and reported no evidence of an association at lag 0 and 1 day. The largest association in terms of magnitude and precision was for lag 2 days (3.8% [95% CI: 0.6, 7.2]). Chen et al. (2011b), within the CAPES study, reported evidence of an immediate effect between short-term PM_{10-2.5} exposure and respiratory mortality by observing evidence of a positive association at lag 1 and no evidence of an association at lag 0 and 2 days. Stafoggia et al. (2017), in a study of eight European cities, examined single-day lags ranging from 0 to 10 days also reported evidence of an immediate effect with positive associations at lags 0 and 1 day. However, the authors found evidence of positive associations at longer lags (i.e., lag 4 and 5), but confidence intervals were wide. The results across the studies that examined a series of single-day lags is further supported by the meta-analysis by Adar et al. (2014) where an examination of single-day lag risk estimates across studies found positive associations across lags ranging from 0 to 2 days with the strongest association in terms of magnitude and precision occurring at lag 1.

Although the studies that examined a series of single-day lags tend to support a PM_{10-2.5}-respiratory mortality association within the first few days after exposure, Samoli et al. (2013), in the MED-PARTICLES project, did not provide further support for this lag structure of associations. The authors examined both a series of multiday lags as well as single-day lags through a polynomial

distributed lag over 0–7 days. In the multiday lag analysis, [Samoli et al. \(2013\)](#) reported the strongest evidence of an association for a delayed effect (i.e., lag 2–5 days) (0.72% [95% CI: –0.31, 1.8]), with no evidence of an association at lag 0–1 days. This observation was confirmed when examining the polynomial distributed lag provided evidence of positive associations only at lags 3, 4, and 5 (quantitative results not presented).

Overall, studies that examined the lag structure of associations generally support that short-term PM_{10–2.5} exposure contributes to respiratory mortality effects within the first few days after exposure, ranging from 0–2 days. However, there is initial evidence that the PM_{10–2.5}-respiratory mortality association may be more delayed.

5.3.7.1.3 Effect Modification

Season

An examination of potential seasonal differences in associations between short-term PM_{10–2.5} exposure and respiratory mortality in the 2009 PM ISA ([U.S. EPA, 2009](#)) was limited to one U.S. multicity study ([Zanobetti and Schwartz, 2009](#)) that provided initial evidence of associations being larger in magnitude in the spring and summer. Although still limited in number, some recent multicity studies conducted an examination of potential seasonal differences in associations ([Lee et al., 2015](#); [Samoli et al., 2013](#)).

[Samoli et al. \(2013\)](#), in the MED-PARTICLES project, only examined warm (April–September) and cold months (October–March). In analyses focusing on lag 0–5 days, the authors observed evidence of positive associations in both seasons, with associations larger in magnitude during the warm season (1.21% [95% CI: –2.0, 4.6]) compared to the cold season (0.30% [95% CI: –1.8, 2.5]), but confidence intervals were wide. [Lee et al. \(2015\)](#), in a study conducted in 11 east Asian cities, observed a different pattern of seasonal associations. The authors reported larger associations in the cold season (1.2% [95% CI: 0.16, 2.3]) compared to the warm (0.42% [95% CI: –0.30, 1.2]). It is unclear why these results differ from the other studies, but mean PM_{10–2.5} concentrations and mean temperature tended to be higher across the cities in [Lee et al. \(2015\)](#) compared to the cities in the other studies evaluated in this section. Overall, the inconsistent evidence across studies does not provide additional information on the seasonal pattern of associations between short-term PM_{10–2.5} exposure and respiratory mortality.

Temperature

In addition to examining whether there is evidence that warm temperatures modify the PM_{10–2.5}-respiratory mortality relationship by conducting seasonal analyses, a recent study also examined whether there is evidence that high temperature days modify the PM_{10–2.5}-respiratory mortality

relationship. Although in all-year analyses, [Pascal et al. \(2014\)](#) reported no evidence of an association between short-term PM_{10-2.5} exposure and respiratory mortality, the authors examined whether temperature modified the relationship. [Pascal et al. \(2014\)](#) examined the impact of temperature on the PM_{10-2.5}-respiratory mortality relationship across nine French cities by comparing associations on warm and nonwarm days, where warm days were defined as those days where the mean temperature exceeded the 97.5th percentile of the mean temperature distribution. When calculating the interaction ratio, which estimated the extra PM effect due to warm days, the authors observed no evidence of a positive modifying effect of warm days on respiratory mortality.

5.3.8 Summary and Causality Determination

Based on a small number of epidemiologic studies observing associations with some respiratory effects and limited evidence from experimental studies to support biological plausibility, the 2009 PM ISA ([U.S. EPA, 2009](#)) concluded that the relationship between short-term exposure to PM_{10-2.5} and respiratory effects is suggestive of a causal relationship. Epidemiologic findings were consistent for respiratory infection and combined respiratory-related diseases, but not for COPD. Studies were characterized by overall uncertainty in the exposure assignment approach and limited information regarding potential copollutant confounding. Controlled human exposure studies of short-term PM_{10-2.5} exposure found no lung function decrements and inconsistent evidence for pulmonary inflammation in healthy individuals or human subjects with asthma. Animal toxicological studies were limited to those using noninhalation (e.g., intra-tracheal instillation) routes of PM_{10-2.5} exposure. Recent studies strengthen the evidence base for asthma exacerbation and respiratory mortality, but they do not rule out chance and confounding. The evidence for the relationship between short-term exposure to PM_{2.5} and effects on the respiratory system is summarized in Table 5-37, using the framework for causality determinations described in the Preamble to the ISAs ([U.S. EPA, 2015](#)).

Table 5-37 Summary of evidence that is suggestive of, but not sufficient to infer, a causal relationship between short-term PM_{10-2.5} exposure and respiratory effects.

Rationale for Causality Determination ^a	Key Evidence ^b	Key References ^b	PM _{10-2.5} Concentrations Associated with Effects ^c
Asthma exacerbation			
Consistent epidemiologic evidence from a limited number of multiple, high quality studies at relevant PM _{2.5} concentrations	Increases in asthma-related hospital admissions and ED visits. Evidence mostly from single-city studies conducted in the U.S.	Section 5.3.2.1	9.7–16.2 µg/m ³

Table 5-37 (Continued): Summary of evidence that is suggestive of, but not sufficient to infer, a causal relationship between short-term PM_{10-2.5} exposure and respiratory effects.

Rationale for Causality Determination ^a	Key Evidence ^b	Key References ^b	PM _{10-2.5} Concentrations Associated with Effects ^c
Uncertainty regarding confounding by copollutants	Potential copollutant confounding for asthma-related hospital admissions and ED visits is examined in a few studies, with some evidence that associations remain robust in models with gaseous pollutants and PM _{2.5} .	Section 5.3.2.1	
Uncertainty regarding exposure measurement error	Uncertainty in using PM _{10-2.5} concentrations, estimated by differencing PM ₁₀ and PM _{2.5} concentrations, as exposure surrogates, is not addressed.		
Limited coherence in epidemiologic studies across the continuum of effects	Providing support for asthma exacerbation are findings of associations for respiratory symptoms in children. There is no evidence for association with lung function decrements, and inconsistent evidence for eNO.	Section 5.3.2.2 Section 5.3.2.3 Section 5.3.2.4	
Inconsistent evidence from controlled human exposure studies	In adults with asthma, measures of lung function are unaffected. Results for pulmonary inflammation were inconsistent, with one study finding many effects on immune function.	Section 5.3.2.4.2 Alexis et al. (2014)	90 µg/m ³
Biological plausibility	Evidence from one controlled human exposure study provides biological plausibility with epidemiologic findings for allergic asthma, the most common asthma phenotype in children.		
Respiratory mortality			
Consistent epidemiologic evidence from multiple, high quality studies at relevant PM _{10-2.5} concentrations	Associations are observed in single and multicity studies, with effects tending to occur between 0–2 days.	Section 5.3.7	
Uncertainty regarding confounding by copollutants and exposure measurement error	Potential copollutant confounding is examined in a few studies, with some evidence that associations remain robust in models with PM _{2.5} .	Section 5.3.7	
Uncertainty regarding exposure measurement error	Uncertainty in using PM _{10-2.5} concentrations, estimated by differencing PM ₁₀ and PM _{2.5} concentrations, as exposure surrogates, is not addressed.	Section 3.3.1	

Table 5-37 (Continued): Summary of evidence that is suggestive of, but not sufficient to infer, a causal relationship between short-term PM_{10-2.5} exposure and respiratory effects.

Rationale for Causality Determination ^a	Key Evidence ^b	Key References ^b	PM _{10-2.5} Concentrations Associated with Effects ^c
Some coherence with underlying causes of mortality	COPD and respiratory infection evidence provide some coherence.	Section 5.3.3 Section 5.3.4	
Exacerbation of COPD, respiratory infection and combined respiratory-related diseases			
Limited epidemiologic evidence and uncertainty regarding PM _{10-2.5} independent effects	Generally positive associations for COPD-related hospital admissions in a limited number of studies conducted in the U.S., Canada, and Asia. Evidence is inconsistent for COPD ED visits.	Section 5.3.3.1	5.6–24.8 µg/m ³
	Generally positive associations ED visits for acute respiratory infection, pneumonia, and combinations of respiratory infections in a limited number of studies in the U.S., Canada, and Asia.	Section 5.3.4.1	5.6–24.8 µg/m ³
	Generally positive associations are observed for combined respiratory-related disease hospital admissions in single-city and multicity studies conducted in the U.S., Canada, and Europe. Evidence is inconsistent for combined respiratory-related disease visits.	Section 5.3.5	
Respiratory effects in healthy populations			
Inconsistent evidence from epidemiologic studies	A limited number of panel studies in healthy adults reported inconsistent evidence of associations with lung function and pulmonary inflammation.	Section 5.3.6.1	
Inconsistent evidence from controlled human exposure studies	Evidence is inconsistent for pulmonary inflammation.	Section 5.3.6.2 Behbod et al. (2013)	235 µg/m ³
Some evidence from toxicological studies at relevant concentrations	Results show altered lung function and pulmonary inflammation in rodents exposed by inhalation to PM _{10-2.5} CAPs.	Amatullah et al. (2012) Aztatzi-Aguilar et al. (2015)	32–793 µg/m ³

^aBased on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble to the ISAs (U.S. EPA, 2015).

^bDescribes the key evidence and references, supporting or contradicting, contributing most heavily to causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where full body of evidence is described.

^cDescribes the PM_{2.5} concentrations with which the evidence is substantiated.

Recent epidemiologic findings more consistently link PM_{10-2.5} to asthma exacerbation than studies reported in the 2009 PM ISA (U.S. EPA, 2009). These studies of hospital admission and ED visits include children older than 5 years. These findings are supported by epidemiologic studies observing respiratory symptoms in children and by a controlled human exposure study showing PM-related effects on inflammation and the immune system. There is limited evidence that associations remain robust in models with gaseous pollutants and PM_{2.5}. Recent, but limited, epidemiologic findings are also more consistent for COPD exacerbation and combined respiratory-related diseases compared with studies reported in the 2009 PM ISA. However, the evidence for COPD hospital admissions is inconsistent across several U.S. cities and for direct PM_{10-2.5} measurements. Recent epidemiologic findings for respiratory infection differ than findings reported in the 2009 ISA in that they indicate associations with pneumonia, but not combinations of respiratory infections. The respiratory effects related to short-term PM_{10-2.5} exposure in healthy individuals remain inconsistent, although some controlled human exposure and animal toxicological studies show effects. The evidence base for respiratory mortality is expanded since the 2009 PM ISA (U.S. EPA, 2009) and is generally supportive of associations with short-term exposure to PM_{10-2.5}. Studies provide initial evidence that PM_{10-2.5}-respiratory mortality associations remain positive but may be attenuated in copollutant models. In addition, PM_{10-2.5} effects on respiratory mortality tend to occur within the first few days of exposure (i.e., lags 0 to 2 days). Across most of these respiratory outcome groups, copollutant confounding remains uncertain. An uncertainty spanning all epidemiologic studies examining associations with PM_{10-2.5} is the lack of a systematic evaluation of the various methods used to estimate PM_{10-2.5} concentrations and the resulting uncertainty in the spatial and temporal variability in PM_{10-2.5} concentrations compared to PM_{2.5} (Section 2.5.1.2.3 and Section 3.3.1.1). **Overall, the collective evidence is suggestive of, but not sufficient to infer, a causal relationship between short-term PM_{10-2.5} exposure and respiratory effects.**

5.4 Long-Term PM_{10-2.5} Exposure and Respiratory Effects

The 2009 PM ISA concluded that the evidence was inadequate to assess the relationship between long-term exposure to PM_{10-2.5} and respiratory effects (U.S. EPA, 2009).⁶⁰ At that time, the evidence consisted of a single epidemiologic study. Some recent epidemiologic findings link PM_{10-2.5} to lung function metrics (Section 5.4.2), the development of asthma (Section 5.4.3), and respiratory infection (Section 5.4.5) in children. However, there is little or no evidence for the development of allergic disease (Section 5.4.4), severity of asthma (Section 5.4.6), or respiratory effects in healthy populations (Section 5.4.7). In all recent studies, PM_{10-2.5} concentrations were estimated by LUR models, dispersion models, or by subtracting monitored PM_{2.5} concentrations from monitored PM₁₀ concentrations. The major uncertainties for these studies involve the potential for exposure measurement error, especially

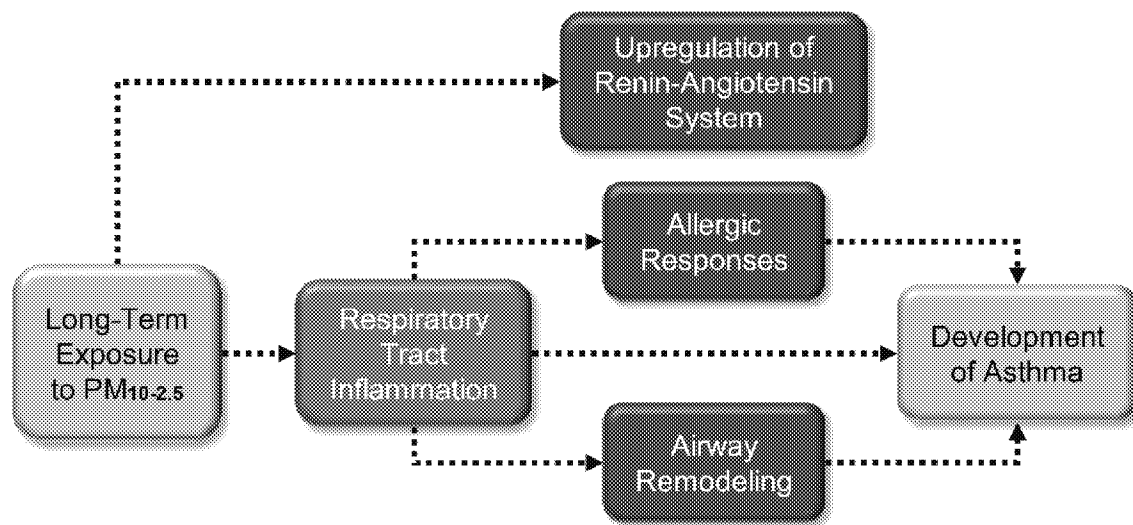
⁶⁰ As detailed in the Preface, risk estimates are for a 5 µg/m³ increase in annual PM_{10-2.5} concentrations unless otherwise noted.

relating to the errors due to subtracting PM_{2.5} concentration from PM₁₀ concentration, notably when the monitors are not collocated, and the potential for confounding related to copollutants. Experimental evidence is limited to a single inhalation exposure in healthy animals, although additional studies using noninhalation routes of exposure provide biological plausibility for a relationship between long-term exposure to PM_{10-2.5} and asthma severity.

5.4.1 Biological Plausibility

This section describes biological pathways that potentially underlie respiratory health effects resulting from long-term exposure to PM_{10-2.5}. [Figure 5-48](#) graphically depicts the proposed pathways as a continuum of upstream events, connected by arrows, that may lead to downstream events observed in epidemiologic studies. This discussion of “how” long-term exposure to PM_{10-2.5} may lead to respiratory health effects contributes to an understanding of the biological plausibility of epidemiologic results evaluated later in [Section 5.4](#).

Once PM_{10-2.5} deposits in the respiratory tract, it may be retained, cleared, or solubilized (see [CHAPTER 4](#)). Insoluble and soluble components of PM_{10-2.5} may interact with cells in the respiratory tract, such as epithelial cells, inflammatory cells, and sensory nerve cells. One way in which this may occur is through reduction-oxidative (redox) reactions. As discussed in [Section 2.3.3](#), PM may generate reactive oxygen species (ROS) and this capacity is termed “oxidative potential.” Furthermore, cells in the respiratory tract may respond to the presence of PM by generating ROS. Further discussion of these redox reactions, which may contribute to oxidative stress, is found in [Section 5.1.1](#) of the 2009 PM ISA (U.S. EPA, 2009). In addition, poorly soluble particles may translocate to the interstitial space beneath the respiratory epithelium and accumulate in the lymph nodes (see [CHAPTER 4](#)). Immune system responses due to the presence of particles in the interstitial space may contribute to respiratory health effects.



Note: The boxes above represent the effects for which there is experimental or epidemiologic evidence, and the dotted arrows indicate a proposed relationship between those effects. Progression of effects is depicted from left to right and color-coded (gray, exposure; green, initial event; blue, intermediate event; orange, apical event). Here, apical events generally reflect results of epidemiologic studies, which often observe effects at the population level. Epidemiologic evidence may also contribute to upstream boxes. When there are gaps in the evidence, there are complementary gaps in the figure and the accompanying text below.

Figure 5-48 Potential biological pathways for respiratory effects following long-term PM_{10-2.5} exposure.

Evidence that long-term exposure to PM_{10-2.5} may affect the respiratory tract generally informs one proposed pathway (Figure 5-48). It begins with respiratory tract inflammation and leads to allergic responses and airway remodeling that may underly the development or worsening of asthma. Epidemiologic evidence links long-term exposure to PM_{10-2.5} and eNO, a marker of airway inflammation (Dales et al., 2008). Supportive evidence is provided by several animal toxicological studies involving intra-tracheal instillation (Liu et al., 2014; He et al., 2013a; He et al., 2013b). In these studies, multiple exposures to dust storm-associated PM_{10-2.5} resulted in allergic inflammation and airway remodeling in nonallergic mice and enhanced allergen-induced responses in allergic mice. These findings are supportive of a link between long-term PM_{10-2.5} exposure and incident asthma (Section 5.4.3). This proposed pathway provides biological plausibility for epidemiologic evidence of respiratory health effects and will be used to inform a causality determination, which is discussed later in the chapter (Section 5.4.9).

In addition, a study of long-term PM_{10-2.5} exposure in animals (Aztatzi-Aguilar et al., 2015) found decreases in tissue levels of heme oxygenase-1 and IL-6, markers of oxidative stress and inflammation, respectively. Increases in mRNA and protein levels of angiotensin receptor Type 1 and mRNA levels of angiotensin converting enzyme, which are components of the RAS, were also observed. Angiotensin receptor Type 1 mediates the effects of angiotensin II, which is a potent vasoconstrictor and mediator in the vasculature. Deposition of inhaled PM_{10-2.5} is expected to primarily occur in the extrathoracic airways

(i.e., the nose) of rodents and to result in a much smaller fraction deposited in the lower respiratory tract compared with humans. This study links deposition of PM_{10-2.5} in the nose to increased activity of the RAS and to a possible dampening of oxidative stress and inflammation in the lung.

5.4.2 Lung Function and Lung Development

As evaluated in the 2009 PM ISA (U.S. EPA, 2009), a cross-sectional analysis of 1,613 schoolchildren in Windsor, Ontario reported that a 5 ug/m³ increase in PM_{10-2.5} was not associated with percent predicted FEV₁ (0.26 [95% CI: -4.22, 4.74]) and was associated with small, imprecise (i.e., wide 95% CIs) increase in percent predicted FVC: (1.10 [95% CI: -8.11, 10.39]) (Dales et al., 2008). Recent analyses of European birth cohorts have observed consistent associations between PM_{10-2.5} and an array of lung function metrics. In the PIAMA cohort, PM_{10-2.5} estimated at children's current addresses was associated with decreases in FEV₁, FVC, and FEF₂₅₋₇₅ measures collected at age 8 and 12 (Gehring et al., 2015a). Similarly, in an ESCAPE project analysis of five European cohorts, PM_{10-2.5} estimates at both birth address and current address were negatively associated with FEV₁ measured at ages 6 and 8, but the effect was stronger when current address was used in the exposure assignment (Gehring et al., 2013). PM_{10-2.5} at current address was also associated with higher odds of FEV₁ <85% of predicted values (OR: 1.81 [95% CI: 0.94, 3.47]), a clinically significant indicator of impaired lung function.

Cross-sectional studies of schoolchildren in 24 Taiwanese provinces (Chen et al., 2015a) and 9–10-year olds participating in the Child Heart and Health Study in England (Barone-Adesi et al., 2015) provided inconsistent evidence of an association between PM_{10-2.5} and lung function. While Chen et al. (2015a) reported reductions of 102 ml (95% CI: 16, 189 ml) in FEV₁ and 121 ml (95% CI: 15, 227 ml) in FVC per 5 µg/m³ increase in PM_{10-2.5} over the past 2 months, Barone-Adesi et al. (2015) did not observe any associations between annual PM_{10-2.5} exposure and the same lung function metrics. Additionally, it is unclear whether Chen et al. (2015a) estimated PM_{10-2.5} using collocated PM₁₀ and PM_{2.5} monitors.

In addition to studies conducted among children, one epidemiologic study evaluated the effects of long-term exposure to PM_{10-2.5} on pulmonary function in adults. Results for the various indices of pulmonary function were inconsistent among adults participating in the ESCAPE project (Adam et al., 2015). PM_{10-2.5} was associated with decrements in FEV₁ and FVC in a cross-sectional analysis, but an increase in FEV₁ in longitudinal analyses. Due to the strengths of a longitudinal study design compared to a cross-sectional design, it's possible that the negative association may have been the result of unmeasured confounding in the cross-sectional analysis.

5.4.3 Development of Asthma

1 There were no studies examining the association between long-term exposure to PM_{10-2.5} and the
2 development of asthma available for inclusion in the 2009 PM ISA (U.S. EPA, 2009). A few recent
3 studies report associations between PM_{10-2.5} and asthma incidence. In the PIAMA cohort in the
4 Netherlands (Gehring et al., 2015a) and a pooled analysis of four European birth cohorts (Gehring et al.,
5 2015b), asthma incidence was associated with PM_{10-2.5} concentrations outside birth residences. The
6 associations were attenuated, but still positive when PM_{10-2.5} concentrations were assigned at the address
7 of the participant at the time of follow-up. This indicates the potential importance of early life exposures.

8 Studies examining asthma prevalence in children reported contrasting evidence. The Gehring et
9 al. (2015b) pooled analysis, discussed above, observed inconsistent evidence of an association across
10 cohorts, and reported a null association in a meta-analysis combining results from all cohorts. Another
11 ESCAPE project analysis of five European birth cohorts estimated PM_{10-2.5} at participants' birth addresses
12 and addresses at age 4 and age 8 (Möller et al., 2014). Birth and current address PM_{10-2.5} was not
13 associated with higher odds of prevalent asthma at age 4. However, PM_{10-2.5} estimated at both birth and
14 current address was associated with an increase in odds of asthma by age 8. Contrary to the results for
15 asthma incidence, the association was higher in magnitude and more precise when asthma prevalence was
16 related to current address PM_{10-2.5} concentrations (OR: 1.16 [95% CI: 0.93, 1.44]) rather than birth
17 address exposure (1.10 [0.72, 1.69]).

18 No recent studies have examined subclinical effects underlying the development of asthma in
19 association with long-term exposure to PM_{10-2.5}. A cross-sectional analysis of 1,613 schoolchildren in
20 Windsor, Ontario, reviewed in the 2009 PM ISA (U.S. EPA, 2009), reported a null association between
21 PM_{10-2.5} and Ln(eNO) (Dales et al., 2008). Results from a prior CHS analysis (Bastain et al., 2011)
22 showed that elevated eNO was associated with increased risk of new onset asthma.

23 In addition to studies conducted among children, one epidemiologic study evaluated the effects of
24 long-term PM_{10-2.5} exposure in adults. An ESCAPE project analysis also examined associations between
25 PM_{10-2.5} and incident asthma (Jacquemin et al., 2015). In a meta-analysis of all cohorts, annual PM_{10-2.5}
26 was not associated with higher odds of incident asthma (OR: 0.99 [95% CI: 0.87, 1.14]).

27 Animal toxicological studies related to the development of asthma are typically conducted in
28 nonallergic animal models. Inhalation exposure of rodents to PM_{10-2.5} is technically difficult since rodents
29 are obligatory nasal breathers. A group of recent studies examined the effects of long-term PM_{10-2.5} using
30 Asian sand dust and noninhalation routes of exposure (i.e., intra-tracheal instillation). Results provide
31 biological plausibility for a potential role of PM_{10-2.5} in allergic inflammation and airway remodeling (Liu
32 et al., 2014; He et al., 2013a; He et al., 2013b).

5.4.4 Development of Allergic Disease

1 There were no studies examining the association between long-term exposure to PM_{10-2.5} and the
2 development of allergic disease available for inclusion in the 2009 PM ISA (U.S. EPA, 2009). A small
3 number of recent epidemiologic studies examined the association between long-term exposure to PM_{10-2.5}
4 and allergic disease. The relation between early-life exposure to PM_{10-2.5} and allergic sensitization at age
5 4 and 8 years was examined in the ESCAPE pooled analysis of five European cohorts (Gruzieva et al.,
6 2014). There were no clear associations between PM_{10-2.5} concentrations estimated at birth address and
7 sensitization at age 4 or age 8. Similarly, another European birth cohort pooled analysis did not observe
8 an association between PM_{10-2.5} and rhinoconjunctivitis (Gehring et al., 2015b). The PIAMA cohort
9 reported on associations between PM_{10-2.5} and allergic outcomes (Gehring et al., 2015a) noting that
10 PM_{10-2.5} was associated with increases in self-reported hay fever, rhinitis and allergic sensitization during
11 the first 11 years of life (ORs ranging from 1.3 to 1.6 per 5 µg/m³ increase). In a 2006 U.S. National
12 Health Interview Survey (NHIS) cross-sectional analysis, PM_{10-2.5} was examined as a potential predictor
13 of allergy in children aged 3–17 years living within 20 miles of an air-quality monitor (Parker et al.,
14 2009). PM_{10-2.5} was not associated with respiratory allergy/hay fever.

5.4.5 Respiratory Infection

15 There were no studies examining the association between long-term exposure to PM_{10-2.5} and
16 respiratory infection available for inclusion in the 2009 PM ISA (U.S. EPA, 2009). Recently, an ESCAPE
17 project study examined respiratory infections in relation to PM_{10-2.5} (MacIntyre et al., 2014b). PM_{10-2.5}
18 estimated at birth residence was associated with an imprecise increase in odds of pneumonia in the first
19 36 months of life (OR: 1.24 [95% CI: 1.03, 1.5] per 5 µg/m³ increase), but was not associated with
20 increased odds of otitis media or croup. A sensitivity analysis looking at alternative outcome windows
21 showed the strongest association between long-term PM_{10-2.5} and pneumonia diagnosed in the first year of
22 life (OR: 1.46 [95% CI: 1.11, 1.92]). The association between PM_{10-2.5} and pneumonia at 36 months was
23 attenuated, but still positive in a two-pollutant model adjusting for NO₂ (1.13 [0.72, 1.76]; $r = 0.34-0.93$).

5.4.6 Severity of Asthma

24 There were no studies examining the association between long-term exposure to PM_{10-2.5} and
25 severity of asthma available for inclusion in the 2009 PM ISA (U.S. EPA, 2009). Recent studies are
26 limited in number. In an epidemiologic study conducted in northern California, Balmes et al. (2014)
27 examined the association between annual PM_{10-2.5} and symptomatic asthma in a cross-sectional cohort
28 study of adults with both asthma and allergies. The middle and highest tertiles of annual PM_{10-2.5}
29 exposure (10.68–12.68 and ≥12.71 µg/m³, respectively) were not associated with increased odds of
30 asthma symptoms compared to the lowest tertile of exposure (<10.68 µg/m³).

1 Animal toxicological studies related to asthma severity are typically conducted in allergic animal
2 models, which share phenotypic features with asthma (see [Section 5.1.2.4](#)). Inhalation exposure of rodents
3 to PM_{10-2.5} is technically difficult since rodents are obligatory nasal breathers. A group of recent studies
4 examined the effects of long-term PM_{10-2.5} using Asian sand dust and noninhalation routes of exposure
5 (i.e., intra-tracheal instillation). Results provide biological plausibility for a potential role of PM_{10-2.5} in
6 enhancing allergic responses ([Liu et al., 2014](#); [He et al., 2013a](#); [He et al., 2013b](#)).

5.4.7 Subclinical Effects in Healthy Populations

7 Animal toxicological and epidemiologic studies provide evidence for subclinical effects
8 potentially underlying the development of respiratory disease in healthy populations. As reported in the
9 2009 PM ISA ([U.S. EPA, 2009](#)), [Dales et al. \(2008\)](#) found a positive association between long-term
10 exposure to PM_{10-2.5} and eNO, a marker of inflammation, in an epidemiologic study among children
11 living in Windsor, ON. In a recent animal toxicological study, [Aztatzi-Aguilar et al. \(2015\)](#) evaluated
12 pulmonary oxidative stress and inflammatory responses in Sprague Dawley rats exposed for 8 weeks to
13 PM_{10-2.5} CAPs in Mexico City. A decrease in lung tissue heme oxygenase-1 activity was found ($p < 0.05$),
14 but there was no change in γ -glutamyl cysteine synthetase catalytic subunit, another index of oxidative
15 stress. Long-term exposure to PM_{10-2.5} CAPs also resulted in a decrease in IL-6 protein ($p < 0.05$) and
16 changes in the RAS. An increase in angiotensin receptor Type 1 protein was observed along with a
17 decrease in its mRNA levels in lung tissue ($p < 0.05$). Angiotensin receptor Type 1 mediates the effects of
18 angiotensin II, which is a potent vasoconstrictor and mediator in the vasculature. Protein and mRNA
19 levels of angiotensin converting enzyme, which catalyzes the conversion of angiotensin I to angiotensin
20 II, increased following long-term exposure to PM_{10-2.5} CAPs ($p < 0.05$). Since deposition of inhaled
21 PM_{10-2.5} is expected to primarily occur in the extrathoracic airways (i.e., the nose) of rodents, this study
22 links deposition in the nose to increased activity of the RAS and to a possible dampening of oxidative
23 stress and inflammation in the lower airways. Additional study details are found in Table 5-38.

Table 5-38 Study-specific details from an animal toxicological study of long-term exposure to PM_{10-2.5} and respiratory effects in healthy animals.

Study/Study Population	Pollutant	Exposure	Endpoints
<u>Aztatzi-Aguilar et al. (2015)</u> Species: Rat Sex: Male Strain: Sprague Dawley Age/Weight:	PM _{10-2.5} CAPs Mexico City Particle size: PM _{10-2.5} Control: Filtered air	Route: Inhalation Dose/Concentration: Coarse PM _{10-2.5} 32 µg/m ³ Duration: Acute 5 h/day, 3 days Subchronic 5 h/day, 4 days/week, 8 weeks Time to analysis: 24 h	Gene and protein expression in lung tissue <ul style="list-style-type: none"> • IL-6 • Components of RAS and kalikrein-kinin endocrine system • Heme oxygenase-1

IL-6 = interleukin 6; RAS = renin-angiotensin system.

5.4.8 Respiratory Mortality

Two recent European cohort studies evaluated the association between long-term PM_{10-2.5} exposure and mortality and observed inconsistent results. In a pooled analysis of 22 cohorts from 13 European cohorts, Dimakopoulou et al. (2014) observed a null association with respiratory mortality in the ESCAPE cohort. In a French cohort, Bentayeb et al. (2015) observed a positive association between long-term PM_{10-2.5} exposure and respiratory mortality. Both studies used statistical models to predict area-wide PM₁₀ and PM_{2.5} concentrations and used the subtraction method to estimate PM_{10-2.5} concentrations, which contributes to uncertainty regarding exposure measurement error.

5.4.9 Summary and Causality Determination

Based on limited epidemiologic evidence demonstrating associations with some respiratory effects and a lack of evidence from experimental studies to support biological plausibility, the 2009 PM ISA (U.S. EPA, 2009) concluded that evidence was inadequate to assess the relationship between long-term exposure to PM_{10-2.5} and respiratory effects. The evidence characterizing the relationship between long-term exposure to PM_{10-2.5} and respiratory effects is detailed below (Table 5-39), using the framework for causality determinations described in the Preamble to the ISAs (U.S. EPA, 2015). A limited number of recent epidemiology studies expand the evidence base for decrements in lung function, the development of asthma, and respiratory infection in children. Uncertainty regarding copollutant confounding and exposure measurement error results in an inability to rule out chance and confounding. An animal toxicological study examined the potential for inhalation of PM_{10-2.5} to affect the respiratory

1 system and found upregulation of the RAS and a dampening of oxidative stress and inflammation in the
2 lung. Several animal toxicological studies involving noninhalation routes of exposure found allergic
3 inflammation and airway remodeling, which provides biological plausibility for the development of
4 asthma. Overall, **the evidence is inadequate to infer the presence or absence of a causal relationship**
5 **between long-term PM_{10-2.5} exposure and respiratory effects.**

Table 5-39 Summary of evidence that is inadequate to infer the presence or absence of a causal relationship between long-term PM_{10-2.5} exposure and respiratory effects.

Rationale for Causality Determination ^a	Key Evidence ^b	Key References ^b	PM _{2.5} Concentrations Associated with Effects ^c
Limited epidemiologic evidence from multiple, high quality studies at relevant PM _{10-2.5} concentrations	Decrements in attained lung function in children consistently observed in a limited number of cohort studies.	Gehring et al. (2013) Gehring et al. (2015a)	7.6–8.4 µg/m ³
	Increases in asthma incidence in children in a limited number of cohort studies. Supporting evidence from studies of asthma prevalence in children are inconsistent.	Gehring et al. (2015b) Gehring et al. (2015a)	8.4 µg/m ³
Coherence provided by epidemiologic studies of airway inflammation	Results from a single study show an association with eNO in children.	Dales et al. (2008)	7.3 µg/m ³
Uncertainty regarding confounding by copollutants	Potential copollutant confounding is not addressed.		
Uncertainty regarding exposure measurement error	Studies rely on subtraction method to estimate exposure to PM _{10-2.5} adding uncertainty to the interpretation of effect estimates.	Section 3.3.1	
Biological plausibility	Evidence from a few animal toxicological studies involving intra-tracheal exposure provides biological plausibility for limited epidemiologic findings of the development of asthma.	Section 5.4.1	
Limited evidence from a toxicological study at relevant concentrations	Results from a single inhalation study in rodents show respiratory effects.	Aztatzi-Aguilar et al. (2015)	32 µg/m ³

^aBased on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble to the ISAs (U.S. EPA, 2015).

^bDescribes the key evidence and references, supporting or contradicting, contributing most heavily to causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where full body of evidence is described.

^cDescribes the PM_{2.5} concentrations with which the evidence is substantiated.

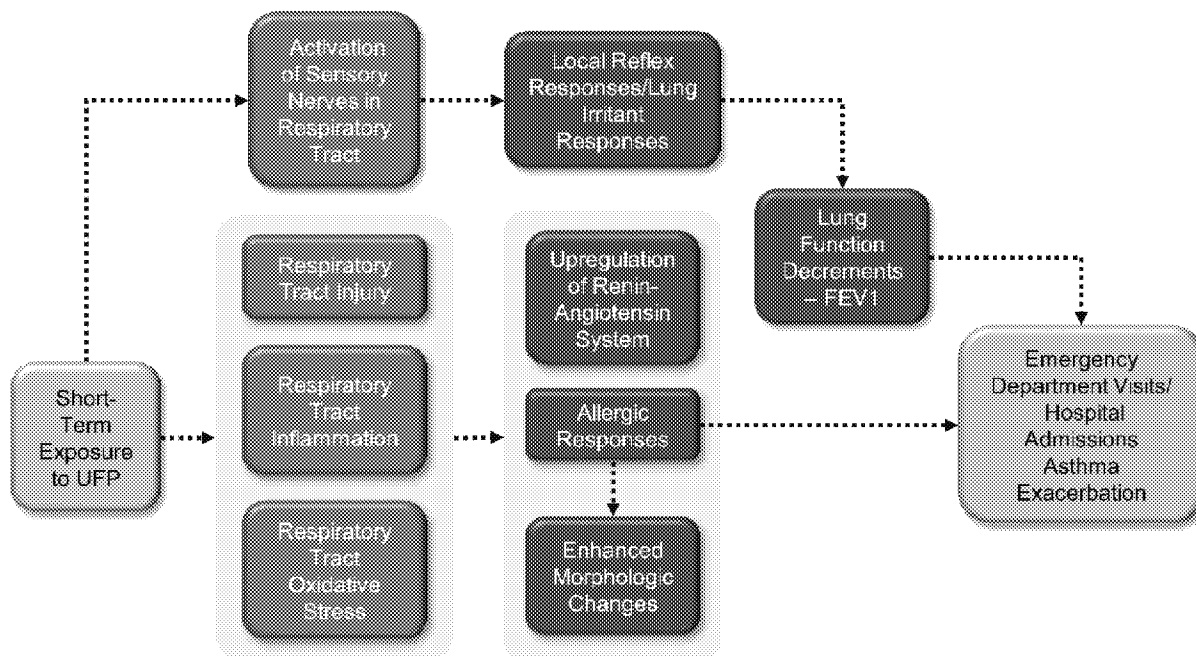
5.5 Short-Term UFP Exposure and Respiratory Effects

1 The 2009 PM ISA concluded that the relationship between short-term exposure to UFP and
2 respiratory effects is “suggestive of a causal relationship” (U.S. EPA, 2009). This conclusion was based
3 on limited, but supporting, epidemiologic evidence indicating associations with hospital admissions or
4 ED visits for respiratory-related diseases, respiratory infection, and asthma exacerbation. Also providing
5 support, personal ambient UFP exposure from time spent in high- and low-traffic areas was associated
6 with lung function decrements in adults with asthma. The few available experimental studies provided
7 limited coherence with epidemiologic findings for asthma exacerbation. Experimental studies of healthy
8 human subjects and animals were also limited in number. Despite some evidence indicating a relationship
9 between UFP exposure and respiratory effects, there was substantial uncertainty due to the small evidence
10 base, a heterogeneous array of respiratory endpoints examined, indeterminate adequacy of UFP
11 measurements, and limited biological plausibility.

12 For many respiratory outcomes, recent studies have not changed the overall evidence base. For
13 asthma exacerbation, there continues to be some epidemiologic evidence, which is not entirely consistent,
14 as well as some animal toxicological evidence (Section 5.5.2). Epidemiologic evidence continues to be
15 consistent for respiratory-related diseases (Section 5.5.5) and inconsistent for COPD exacerbation
16 (Section 5.5.3). Unlike findings reported in the 2009 PM ISA (U.S. EPA, 2009), recent findings are
17 inconsistent for respiratory infection (Section 5.5.4). Recent experimental findings in healthy populations
18 and animal models of cardiovascular disease show that short-term UFP exposure affects some respiratory
19 responses in rodents (Section 0 and Section 5.5.7). Epidemiologic findings in healthy populations are
20 inconsistent, including those for personal ambient exposures (Section 0). Evidence for respiratory
21 mortality is limited (Section 5.5.8). Information on confounding by traffic-related copollutants continues
22 to be limited, and inference about an independent effect of UFP exposure is limited because of
23 uncertainty in the representativeness of UFP measurements, assessed mostly at fixed-site monitors.

5.5.1 Biological Plausibility

24 This section describes biological pathways that potentially underlie respiratory effects resulting
25 from short-term exposure to UFP. Figure 5-49 graphically depicts the proposed pathways as a continuum
26 of upstream events, connected by arrows, that may lead to downstream events observed in epidemiologic
27 studies. This discussion of “how” short-term exposure to UFP may lead to respiratory effects contributes
28 to an understanding of the biological plausibility of epidemiologic results evaluated later in Section 5.5.



Note: The boxes above represent the effects for which there is experimental or epidemiologic evidence, and the dotted arrows indicate a proposed relationship between those effects. Shading around multiple boxes denotes relationships between groups of upstream and downstream effects. Progression of effects is depicted from left to right and color-coded (gray, exposure; green, initial event; blue, intermediate event; orange, apical event). Here, apical events generally reflect results of epidemiologic studies, which often observe effects at the population level. Epidemiologic evidence may also contribute to upstream boxes. When there are gaps in the evidence, there are complementary gaps in the figure and the accompanying text below.

Figure 5-49 Potential biological pathways for respiratory effects following short-term UFP exposure.

Once UFP deposits in the respiratory tract, it may be retained, cleared, or solubilized (see CHAPTER 4). UFP and its soluble components may interact with cells in the respiratory tract, such as epithelial cells, inflammatory cells, and sensory nerve cells. One way in which this may occur is through reduction-oxidative (redox) reactions. As discussed in Section 2.3.3, PM may generate ROS and this capacity is termed “oxidative potential.” Furthermore, cells in the respiratory tract may respond to the presence of PM by generating ROS. Further discussion of these redox reactions, which may contribute to oxidative stress, is found in Section 5.1.1 of the 2009 PM ISA (U.S. EPA, 2009). In addition, poorly soluble particles may translocate to the interstitial space beneath the respiratory epithelium and accumulate in the lymph nodes (see CHAPTER 4). Immune system responses due to the presence of particles in the interstitial space may contribute to respiratory health effects.

Although all size fractions of PM may contribute to oxidative stress, UFPs may contribute disproportionately more as a function of their mass due to their large surface/volume ratio. The relative enrichment of redox active surface components, such as metals and organics, per unit mass may translate

1 to a relatively greater oxidative potential of UFPs compared with larger particles with similar surface
2 components. In addition, the greater surface per unit volume may deliver relatively more adsorbed soluble
3 components to cells. These components may undergo intra-cellular redox cycling following cellular
4 uptake. Furthermore, per unit mass, UFPs may have more opportunity to interact with cell surfaces due to
5 their greater surface area and their greater particle number compared with larger PM. These interactions
6 with cell surfaces may lead to ROS generation, as described in Section 5.1.1 of the 2009 PM ISA (U.S.
7 EPA, 2009). Recent studies have also demonstrated that UFPs have the capacity to cross cellular
8 membranes by nonendocytic mechanisms involving adhesive interactions and diffusion, as described in
9 CHAPTER 4. This may allow UFPs to interact with or penetrate intra-cellular organelles.

10 Evidence that short-term exposure to UFP may affect the respiratory tract generally informs two
11 proposed pathways (Figure 5-49). The first pathway begins with injury, inflammation, and oxidative
12 stress responses, which are difficult to disentangle. Inflammation generally occurs as a consequence of
13 injury and oxidative stress, but it may also lead to further oxidative stress and injury due to secondary
14 production of ROS by inflammatory cells. The second pathway begins with the activation of sensory
15 nerves in the respiratory tract that can trigger local reflex responses and transmit signals to regions of the
16 central nervous system that regulate autonomic outflow.

Injury, Inflammation, and Oxidative Stress

17 Experimental evidence that short-term exposure to UFP affects the respiratory tract is provided
18 by numerous studies and supports a role for injury, inflammation, and oxidative stress. A few studies
19 demonstrate markers of injury (i.e., decreased CC16 protein) and oxidative stress (4-hydroxynoneal,
20 3-nitrotyrosine, Ym1) (Cheng et al., 2016; Li et al., 2010; Kooter et al., 2006). Seagrave et al. (2008)
21 exposed rats to GE containing UFP and found increased lung tissue chemiluminescence that was not
22 present when GE was filtered, indicating that the particulate fraction played a role in the oxidative stress
23 response. In the study by Cheng et al. (2016), a time-course analysis demonstrated oxidative stress in
24 olfactory epithelium after a single exposure of 5 hours, as well as after multiple exposures over 3 weeks.
25 Inflammatory responses were seen in some studies (Cheng et al., 2016; Aztatzi-Aguilar et al., 2015), but
26 not others (Tyler et al., 2016; Amatullah et al., 2012). In Tyler et al. (2016), evidence for inflammation
27 was found in a model of cardiovascular disease but not in healthy animals. In Cheng et al. (2016), time
28 course analysis showed that inflammatory responses occurred concomitantly with oxidative stress
29 responses.

30 Inflammation was not seen in human subjects with asthma following short-term exposure to UFP
31 (Gong et al., 2008). However, supportive evidence for enhancement of allergic responses is provided by a
32 study in human subjects with allergic asthma who were exposed to ultrafine carbon (Schaumann et al.,
33 2014). Enhancement of allergic responses was also found in two studies in animals (Li et al., 2010;
34 Kleinman et al., 2005). In Li et al. (2010), intra-nasal cosensitization with OVA and UFP was required for
35 exacerbation of responses to inhaled UFP and OVA. These responses included increased BALF

eosinophils and neutrophils, upregulation of Th2 and Th17 cytokines, increased plasma OVA-specific IgE, and enhanced morphologic changes that extended to more distal parts of the lung. These results are consistent with some epidemiologic evidence of asthma-related hospital admissions and ED in association with UFP concentrations (Section 5.5.2.1).

Activation of Sensory Nerves

Short-term exposure to UFP did not alter pulmonary function in animal studies (Amatullah et al., 2012; Seagrave et al., 2008). However, in human subjects with asthma, decreases in FEV₁ and oxygen saturation were observed (Gong et al., 2008). Although lung irritant responses can sometimes result in decreased FEV₁, it is not clear whether inhalation of PM_{2.5} led to FEV₁ changes by this pathway or whether it was mediated by inflammation. Epidemiologic panel studies conducted in people with asthma also found associations with lung function decrements (Mirabelli et al., 2015; McCreanor et al., 2007). These results are also consistent with some epidemiologic evidence of asthma-related hospital admissions and ED in association with UFP concentrations (Section 5.5.2.1).

Another study found upregulation of the RAS, as indicated by an increase in mRNA for angiotensin receptor Type 1 and angiotensin converting enzyme, in the lung (Aztatzi-Aguilar et al., 2015). Angiotensin receptor Type 1 mediates the effects of angiotensin II, which is a potent vasoconstrictor and mediator in the vasculature. The SNS and the RAS are known to interact in a positive feedback fashion (Section 8.1.2) with important ramifications in the cardiovascular system. However, it is not known whether SNS activation or some other mechanism mediated the changes in the RAS observed in the respiratory tract in this study.

Summary

As described here, there are two proposed pathways by which short-term UFP exposure may lead to respiratory health effects. One pathway involves respiratory tract inflammation and allergic responses, which are linked to asthma exacerbation. The second pathway involves the activation of sensory nerves in the respiratory tract leading to lung function decrements, which are also linked to asthma exacerbation. While experimental studies involving animals or human subjects contribute most of the evidence of upstream effects, epidemiologic studies found associations between short-term UFP exposure and lung function decrements. Together, these proposed pathways provide biological plausibility for epidemiologic evidence of respiratory health effects and will be used to inform a causality determination, which is discussed later in the chapter (Section 5.5.9).

5.5.2 Asthma Exacerbation

1 In the 2009 PM ISA (U.S. EPA, 2009), the evaluation of the relationship between short-term UFP
2 exposure and asthma exacerbation consisted of a limited number of epidemiologic, controlled human
3 exposure, and animal toxicological studies. Epidemiologic studies provided some evidence of an
4 association between short-term UFP exposure and asthma exacerbation. Evidence for decrements in
5 pulmonary function was found in subjects with asthma in the controlled human exposure study. Evidence
6 for enhanced allergic responses was found in the animal toxicological study in a model of allergic airway
7 disease that shares phenotypic features with asthma.

5.5.2.1 Epidemiologic Studies

8 In the 2009 PM ISA (U.S. EPA, 2009), studies of hospital admissions, ED visits (Andersen et al.,
9 2008b; Halonen et al., 2008), and physician visits (Sinclair and Tolsma, 2004) reported evidence of
10 associations across a range of lags, as well as for different UFP concentration metrics (i.e., number
11 concentration [NC] and surface area [SA]). In panel studies of asthma symptoms in adults with asthma,
12 supporting evidence of asthma exacerbation was observed across size fractions from NC_{10–100} nm to
13 NC_{500–2,500} nm (Mar et al., 2004; von Klot et al., 2002). Supporting evidence was also provided by a study
14 of lung function in adults with asthma in which NC_{10–100} nm was associated with decrements in FEV₁,
15 FVC, FEF_{25–75%}, but not with increases in eNO after walking on a high-traffic road or in a park
16 (McCreanor et al., 2007). This study of scripted exposure minimized uncertainty in the UFP exposure
17 metric by measuring personal ambient UFP at the site of exposure. The evidence across studies was not
18 entirely consistent, as associations between UFP exposure and ED visits for asthma were not observed in
19 the Atlanta-based SOPHIA study (Peel et al., 2005). Additionally, the overall interpretation of results
20 from epidemiologic studies that examined UFP exposures, including those focusing on asthma
21 exacerbation, is complicated by the spatial variability in UFP concentrations, the correlation between
22 UFPs and other traffic-related pollutants, and the various size fractions and concentration metrics used as
23 UFP exposure surrogates.

24 A few recent epidemiologic studies add to those from the 2009 PM ISA (U.S. EPA, 2009) and
25 continue to provide some, but not entirely consistent, support for associations between increases in
26 short-term UFP concentrations exposure and asthma exacerbation. The supporting evidence comes from
27 an array of outcomes related to asthma exacerbation, including hospital admissions, ED visits, and
28 physician visits for asthma to asthma symptoms and medication use. Additional evidence from studies in
29 adults with asthma using personal ambient UFP exposures via scripted exposures in high-traffic locations
30 is more consistent for lung function decrements than pulmonary inflammation. The relatively small body
31 of recent studies of asthma hospital admissions, ED visits, and physician visits examined a range of UFP
32 size fractions, which complicates the interpretation of results across studies. Several studies examined
33 NC_{10–100} nm exposure among older children (>3 years), in whom the ascertainment of asthma is more

1 reliable. All the recent studies used NC to represent UFP exposure; and as detailed in the Preface, when
2 examining the size distribution of particles 67 to 90% of NC contains particles $<0.1\ \mu\text{m}$. Samoli et al.
3 (2016a) reported no association with asthma hospital admissions in a study of five European cities. In
4 contrast, Iskandar et al. (2012) reported an association with $\text{NC}_{10-700\ \text{nm}}$ in a study conducted in
5 Copenhagen, Denmark. Across studies, a similar array of lags was examined and no particular lag was
6 identified as having a stronger association with asthma hospital admissions, but many results support
7 associations with UFP concentrations with a lag of 1 to 5 days or averaged over 3 to 6 days (Table 5-40).
8 While the examination of the relationship between short-term UFP exposure and asthma hospital
9 admissions focused on studies that examined daily changes in UFP concentrations and hospital
10 admissions (e.g., time-series, case-crossover analyses), the assessment of the relationship with ED visits
11 was limited to a study that focused on asthma exacerbations that led to an ED visit (Evans et al., 2014). In
12 a group of children with asthma enrolled in the School-Based Asthma Therapy trial, Evans et al. (2014)
13 examined whether exposure to traffic-related pollutants, including UFPs, resulted in an asthma
14 exacerbation that lead to an ED visit over multiday averages up to 0–7 days. There was some evidence of
15 an association for lag 0–3 days ($\text{OR} = 1.3$ [95% CI: 0.90, 1.8] for a 2,088 increase in UFPs per cm^{-3});
16 however, the association was more evident in children receiving preventative medication at school
17 compared to at home. A recent study examined the association between UFP exposure and lung function
18 and subclinical effects in adults with asthma. In this panel study of 18 adults in Atlanta, GA, NC_{total} was
19 associated with increased eNO and decreased FEV_1 (Mirabelli et al., 2015). Personal NC_{total} was
20 measured during two morning commutes through rush-hour traffic, resulting in higher exposure levels.
21 The observed associations with FEV_1 were consistent across spirometry test conducted 0, 1, 2, and
22 3 hours post-commute, while increased eNO was only associated with UFP exposure in adults with
23 below-median asthma control.

Table 5-40 Epidemiologic studies of UFP and asthma hospital admissions, emergency department (ED) visits, and physician visits.

Study, Location, Years, Age Range	Exposure Assessment	UFP Concentration (particles/cm ³) ^a	Single Pollutant Effect Estimate (95% CI)	Copollutant Examination
Hospital admissions				
<u>Andersen et al. (2008b)</u> Copenhagen, Denmark 2001–2004 5–18 yr	NC _{10–100} nm, NC total and NC with median diameters 12, 23, 57, 212 nm One monitor, within 15 km of hospitals, mean 6 km. <i>r</i> for NC _{total} = 0.62 with roadside monitor 3 km away, 0.80 with rural monitor	NC _{10–100} nm Mean: 6,847 99th: 16,189 NC _{total} Mean: 8,116 99th: 19,895	RR per 3,259 Lag 0–4 NC _{10–100} nm 1.06 (0.97, 1.16) RR per 3,907 NC _{total} 1.07 (0.98, 1.17)	Correlation (<i>r</i>): 0.61 NO ₂ , 0.48 CO, 0.40 PM _{2.5} Copollutant models with: NO ₂ , CO
<u>†Iskandar et al. (2012)</u> Copenhagen, Denmark 2001–2008 0–18 yr	NC _{10–700} nm One monitor, within 15 km of hospitals, mean 6 km	Mean: 6,398 75th: 7,951	OR per 7,004 Lag 0–4 1.06 (0.98, 1.14)	Correlation (<i>r</i>): 0.51 NO ₂ , 0.45 NO _x , 0.26 PM _{2.5} Copollutant models with: NO ₂ , NO _x , PM _{2.5}
<u>†Samoli et al. (2016a)</u> Five European cities 2001–2011 All ages	Barcelona: NC _{5–1,000} nm Copenhagen: NC _{6–700} nm Helsinki: NC _{10–100} nm Rome and Stockholm: NC _{7–3,000} nm One or two sites per city. All urban background sites except for traffic site in Rome	Means Barcelona: 19,554 Copenhagen: 5,105 Helsinki: 7,951 Rome: 34,043 Stockholm: 9,128	Percent increase per 10,000 Lag 1 2.1 (–0.28, 4.6)	Correlation (<i>r</i>): 0.38–0.69 NO ₂ , 0.07–0.67 CO, 0.09–0.57 PM _{2.5} Copollutant models with: NR

Table 5-40 (Continued): Epidemiologic studies of ultrafine particle (UFP) and asthma hospital admissions, emergency department (ED) visits, and physician visits.

Study, Location, Years, Age Range	Exposure Assessment	UFP Concentration (particles/cm ³) ^a	Single Pollutant Effect Estimate (95% CI)	Copollutant Examination
ED visits				
Peel et al. (2005) Atlanta, GA 1998–2000 All ages	NC _{10–100} nm 1 monitor, near city center	Mean: 38,000 90th: 74,600	RR per 30,000 Lag 0–2 1.00 (0.98, 1.02)	Correlation (<i>r</i>): NR Copollutant models with: NR
†Evans et al. (2014) Rochester, NY 2006–2009 3–10 yr	NC _{10–100} nm 1 monitor 1.6–11 km from school, within 15 km of home, 1.5 km of highway.	Mean: 5,151 75th: 6,449 95th: 9,575	OR per 2,008 Lag 0–3 1.27 (0.90, 1.79)	Correlation (<i>r</i>): Warm season = 0.57 O ₃ Copollutant models with: CO, O ₃
Physician visits				
Sinclair and Tolsma (2004) Atlanta, GA 1998–2000 All ages	SC _{10–100} nm 1 monitor, near city center	Mean: 249 µm ² /cm ²	RR per 244 Lag 3–5 1.22 (95 CI NR)	Correlation (<i>r</i>): NR Copollutant models with: NR

CO = carbon monoxide, CI = confidence interval, NC = number concentration, NO₂ = nitrogen dioxide, NO_x = sum of NO₂ and nitric oxide, NR = not reported, O₃ = ozone, OR = odds ratio, RR = relative risk, SC = surface area concentration, SD = standard deviation, SO₂ = sulfur dioxide, UFP = ultrafine particles.

^aAll data are for 24-hour average.

†Studies published since the 2009 PM ISA.

1 The epidemiologic studies of short-term exposure to UFP and asthma hospital admissions each
2 have 1 to 2 monitors per study, covering a 15-km radius in some cases (Table 5-40). Spatial variability in
3 UFP concentration may not be captured over this area, introducing some uncertainty in the exposure
4 surrogate (Section 2.5; Section 3.4.2.2). It is possible that associations are related to similarities in
5 temporal variability of UFP sources throughout study areas, as Sarnat et al. (2010) observed for
6 spatially-variable NO₂, but this remains an uncertainty since spatiotemporal variability across cities has
7 not been well characterized. In addition to major uncertainties regarding the spatial variability in UFP and
8 the various size fractions and concentration metrics used as UFP exposure surrogates, confounding by
9 traffic-related pollutants also remains a concern, as studies have not thoroughly examined potential
10 copollutant confounding. Studies evaluated in the 2009 PM ISA (U.S. EPA, 2009), which focused on
11 both asthma hospital admissions (Andersen et al., 2008b) and lung function changes (McCreanor et al.,
12 2007) in people with asthma, provided initial evidence that UFP associations persisted after adjustment
13 for NO₂ or CO even when UFP was moderately correlated with copollutants [e.g., $r = 0.58$ for personal
14 ambient UFP and NO₂ exposures (McCreanor et al., 2007)]. Recent results show robust UFP associations
15 to adjustment for CO and O₃, but null associations with adjustment for NO₂ or NO_x (Table 5-40).

5.5.2.2 Controlled Human Exposure

16 Only one study evaluated in the 2009 PM ISA (U.S. EPA, 2009) investigated the effects of
17 short-term UFP exposure and respiratory effects in individuals with asthma. In this study, Gong et al.
18 (2008) reported decreases in pulmonary function (oxygen saturation and FEV₁) following a 2-hour
19 exposure to 100 µg/m³ UFP CAPs (less than 0.18 µm aerodynamic diameter). No changes in pulmonary
20 inflammation were found.

5.5.2.3 Animal Toxicological Studies

21 As described in the 2009 ISA for PM (U.S. EPA, 2009), Kleinman et al. (2005) found that a
22 multiday exposure to roadway ultrafine PM (UFP) CAPs in Los Angeles enhanced allergic responses in
23 OVA-sensitized and challenged BALB/c mice, and that this effect was dependent on proximity to the PM
24 source. Recently, Li et al. (2010) extended these observations in OVA-sensitized and challenged BALB/c
25 mice. A hybrid exposure to Los Angeles UFP CAPs was conducted by intra-nasal cosensitization with
26 OVA and UFP (Days 1, 2, and 4), followed 2 weeks later with inhalation exposures to concentrated UFP
27 (Days 18, 19, 22, 23 and 24) that overlapped with intra-nasal OVA challenge (Days 23 and 24). Only
28 mice that were cosensitized with UFP responded to secondary OVA challenges with increases in lavaged
29 eosinophils, plasma OVA-specific IgE, and pulmonary expression of eotaxin, IL-5, IL-13, and Muc5ac
30 ($p < 0.05$). Inhalation exposure to UFP during the challenge phase enhanced these allergic responses
31 compared to filtered air exposed mice ($p < 0.05$). Similarly, UFP exposure during OVA challenge

enhanced neutrophil influx and pulmonary expression of IL-17 and Ym1, a marker of oxidative stress, in mice which were cosensitized with UFP and OVA ($p < 0.05$). These results demonstrate that short-term UFP exposure exacerbated the effects of allergen and suggest the involvement of Th2 and Th17 helper cells in the response. Pulmonary histopathology revealed that UFP inhalation during the OVA challenge extended allergic inflammation to more distal regions of the lung (i.e., the proximal alveolar duct and adjacent alveolar parenchyma). Their small size may have allowed UFPs to evade phagocytosis and deposit in the deep lung due to diffusion, as well as to stick to the airways walls due to Van der Waal's forces. The oxidative potential of urban UFP (Li et al., 2009) may have also contributed to inflammatory responses. It should be noted that in the recent study by Li et al. (2010) PM and allergens were coinstilled during sensitization prior to the inhalation challenge. This study design more clearly demonstrates the exacerbation of allergic responses than adjuvant activity. Short-term exposure to UFP may also promote allergic sensitization and additional experiments employing different study designs are needed to show this effect. Additional study details are found in Table 5-41.

Table 5-41 Study-specific details from an animal toxicological study of short-term exposure to UFP and subclinical effects underlying asthma exacerbation in a model of allergic airway disease.

Study/Study Population	Pollutant	Exposure	Endpoints
Li et al. (2010)	Ultrafine—ambient	Route: Intra-nasal sensitization	PM characterization
Species: Mouse	Los Angeles	with PM and OVA (2 days)	Serum IgE, IgG1
Sex: Female	OVA	Inhalation of PM on days of	BALF cells
Strain: BALB/c	Particle size:	OVA challenge	BALF cytokines
Age/Weight: 8–10 weeks	<0.18 μm	Dose/Concentration: 4 h/day	Histopathology—lung
	Particle mass:	for 5 days	
	101.3 \pm 5.1 $\mu\text{g}/\text{m}^3$		

IgE = immunoglobulin E; IgG1 = immunoglobulin G1; BALF = bronchoalveolar lavage fluid; OVA = ovalbumin.

5.5.3 Chronic Obstructive Pulmonary Disease (COPD) Exacerbation

The 2009 PM ISA (U.S. EPA, 2009) evaluated a small body of literature examining the association between UFP and hospital admissions and ED visits for COPD. The studies evaluated in the 2009 PM ISA, limited to single-cities, provided inconsistent evidence of associations with UFPs. There are a few recent studies of UFP exposure and COPD exacerbation, but the evidence base remains small and does not clearly support a relationship. This applies to COPD hospital admissions and ED visits (Table 5-42), which can result from uncontrollable respiratory symptoms that are hallmarks of COPD

1 exacerbation such as cough, sputum production, and shortness of breath. The uncertain adequacy of the
2 UFP concentration metrics used for exposure surrogates is a major limitation in the evidence base overall.

3 Recently, some studies examined associations with COPD, but they are limited to studies of
4 hospital admissions and again are conducted in individual cities. Recent studies examine COPD hospital
5 admissions in Europe and observe an association in Rome, Italy (Belleudi et al., 2010) but not a multicity
6 study that includes Rome (Samoli et al., 2016a) (Table 5-42). UFP concentrations were averaged over
7 24 hours, and all studies examined an array of lags (up to 10 days). In Rome, Italy, (Belleudi et al., 2010)
8 found evidence of a positive association between UFP and COPD hospital admissions at 0–1-day
9 distributed lag among adults aged 35 years and older (0.95 [95% CI: –0.8, 2.73]). Adjustment for PM₁₀ or
10 for PM_{2.5} did not alter the association of COPD (lag 0) with particle NC (1.9% [95% CI: 0.1, 3.8] and
11 1.3% [95% CI: 0.8, 3.5%], per 10,000 particles/cm³, respectively). There was some evidence that
12 associations were stronger in terms of magnitude and precision in the spring and fall season (3.72% [95%
13 CI: 0.81, 6.70]). Additionally, in a study conducted in Helsinki, Finland, Halonen et al. (2009b) reported
14 an association between COPD hospital admissions in the nucleation mode (<0.03 µm), with an 0.8%
15 (95% CI: –2.28, 3.97) increase in hospital admissions for a 3,583-count increase in the nucleation mode,
16 and a 0.82% (95% CI: –1.51, 3.20) increase in hospital admissions for a 2,467-count increase in the
17 Aitken mode (0.03–0.1 µm) (lag 3). Among adults with COPD in Erfurt, Germany, NC_{10–100} nm was not
18 associated with blood levels of the proinflammatory cells neutrophils and eosinophils or most markers of
19 blood coagulation that are linked to cardiovascular effects rather than COPD (Bruske et al., 2010;
20 Hildebrandt et al., 2009).

21 Epidemiologic studies examining respiratory infection are limited by their UFP exposure
22 assessment, because they relied on data from one or two monitors and thus could not capture the spatial
23 variability in UFP concentrations across study locations (Section 2.5.1, Section 3.4.2.2). Additionally, the
24 limited assessment of potential copollutant confounding complicates the interpretation of results and
25 understanding whether UFPs are independently associated with COPD exacerbations or may be serving
26 as an indicator of highly correlated copollutants.

Table 5-42 Epidemiologic studies of UFP and exacerbation of chronic obstructive pulmonary disease.

Study	Exposure Assessment	Outcome Assessment	UFP Concentration particles/cm ^{3a}	Single Pollutant Effect Estimate 95% CI	UFP Copollutant Model Results and Correlations
Peel et al. (2005) Atlanta, GA 1998–2000	NC _{10–100} nm One monitor, near city center	ED visits All ages Visits concentrated in city center	Mean: 38,000 SD: 40,700 90th: 74,600	RR per 30,000 Lag 0–2 0.98 (0.94, 1.02)	No copollutant model Copollutant correlations NR
†Belleudi et al. (2010) Rome, Italy 2001–2005	NC _{total} Condensation Particle Counter One monitor, 2 km from city center	Hospital admissions Adults ≥35 yr	Mean: 37,456 SD: 21,394 75th: 47,995	RR per 9,392 Lag 0 1.02 (1.00, 1.03)	No copollutant model No copollutants examined <i>r</i> = 0.55 PM _{2.5} .
†Samoli et al. (2016a) Barcelona, Spain; Copenhagen, Denmark; Helsinki, Finland; Rome, Italy; Stockholm, Sweden 2001–2011 across cities	Barcelona: NC _{5–1,000} nm Copenhagen: NC _{6–700} nm Helsinki: NC _{10–100} nm Rome and Stockholm: NC _{7–3,000} nm One or two sites per city. All urban background sites except for traffic site in Rome	Hospital admissions All ages	Means Barcelona: 19,554 Copenhagen: 5,105 Helsinki: 7,951 Rome: 34,043 Stockholm: 9,128	RR per 10,000 Lag 0 0.99 (0.96, 1.02)	No copollutant model <i>r</i> = 0.38–0.69 NO ₂ , 0.07–0.67 CO, 0.09–0.57 PM _{2.5} .

CO = carbon monoxide, CI = confidence interval, ED = emergency department, NC = number concentration, NO₂ = nitrogen dioxide, NR = not reported, PM_{2.5} = particulate matter with a nominal mean aerodynamic diameter ≤2.5 μm, *r* = correlation coefficient, RR = relative risk, SD = standard deviation, ultrafine particles.

^aAll data are for 24-hour average.

†Studies published since the 2009 PM ISA.

5.5.4 Respiratory Infection

Regarding the association between UFP and hospital admissions/ED visits for respiratory infections, the body of literature reviewed in the 2009 PM ISA (U.S. EPA, 2009) was very small and provided no evidence of associations with respiratory infections and was limited to single-city studies. Consistent with the 2009 PM ISA, recent studies are limited in number and focus on examining associations between short-term UFP exposure and respiratory infections in individual cities. In Rome, Italy, Belleudi et al. (2010) found no evidence of an association between UFP (UFPs were measures using particle NC from a single monitor) and lower respiratory tract infection hospital admissions at any lag among adults aged 35 years and older. The effect was positive, but imprecise at lag 2 and lag 3 (0.19% [95% CI: -1.48, 1.90] and 0.29% [95% CI: -1.37, 1.98], per 10,000 particles/cm³, respectively). In a study of UFPs and respiratory hospital admissions in five European cities in 2001–2011, Samoli et al. (2016a) found no overall association using city-specific estimates to obtain pooled estimates but did identify a positive association with hospital admissions during warm months of April–September of 4.27% (95% CI 1.68–6.92) for an increase in 10,000 particles/cm³ (lag 2). This effect estimate was robust to inclusion of CO and NO₂ in the statistical model. Halonen et al. (2009b), in a study conducted in Helsinki, Finland, reported no associations for pneumonia hospital admissions in the nucleation mode (<0.03 µm), but observed a 1.5% (95% CI: -0.72, 3.77) increase in hospital admissions for a 2,467-count increase in the Aitken mode (0.03–0.1 µm) (lag 3). Some similarity of the effect estimates was expected by the authors due to the high correlation between these particle fractions.

The body of literature that studied the association between UFPs and hospital admissions/ED visits for respiratory infection hospital admissions expanded since the 2009 PM ISA (U.S. EPA, 2009) but remains somewhat limited. The available evidence suggests small associations between UFPs and respiratory infections, though the distinct size fractions under analysis in each study make cross-study comparisons difficult. The limited evidence from previous and recent studies does not clearly link short-term UFP exposure to increases in respiratory infection, based largely on hospital admissions, ED visits, and physician visits for URI, pneumonia, or LRI, which combines pneumonia and bronchitis (Table 5-43). There is little information to assess the biological plausibility for the supporting findings. Host defense mechanisms that protect the respiratory tract from pathogens such as mucociliary clearance, alveolar macrophage clearance, or innate and adaptive immunity were not assessed in relation to short-term UFP exposure. For the supporting evidence, information also is lacking on sources of heterogeneity, C-R, and the influence of other traffic-related pollutants.

Table 5-43 Epidemiologic studies of UFP and respiratory infection.

Study	Exposure Assessment	Outcome Assessment	UFP Concentration Particles/cm ^{3a}	Single Pollutant Effect Estimate 95% CI	UFP Copollutant Model Results and Correlations
<u>Peel et al. (2005)</u> Atlanta, GA 1998–2000	NC _{10–100} nm One monitor, near city center	ED visits URI and pneumonia All ages Visits concentrated in city center	Mean: 38,000 SD: 40,700 90th: 74,600	RR per 30,000 Lag 0–2 URI 0.99 (0.97, 1.01) Pneumonia 0.98 (0.95, 1.00)	No copollutant model Copollutant correlations NR
<u>Sinclair et al. (2010)</u> Atlanta, GA 1998–2000	SC _{10–100} nm One monitor, near city center	Physician visits URI and LRI All ages HMOs in city outskirts	Mean: 249 $\mu\text{m}^2/\text{cm}^2$ SD: 244	RR per 244 URI, Lag 3–5 1.04 (95% CI NR) LRI, Lag 0–2 1.10 (95% CI NR)	No copollutant model Copollutant correlations NR
<u>Hälonen et al. (2009b)</u> Helsinki, Finland 1998–2004	NC _{30–100} nm One monitor	Hospital admissions Pneumonia Older adults	Median: 3,628 IQR: 1,309 75th: 4,937	RR per 1,309 Lag 0–4 1.04 (1.00, 1.08)	No copollutant model $r = 0.48 \text{ PM}_{2.5}$, 0.65 NO_2 , 0.41 CO , $0.72 \text{ traffic PM}_{2.5}$
<u>†Belleudi et al. (2010)</u> Rome, Italy 2001–2005	NC _{total} One monitor, 2 km from city center	Hospital admissions LRI Adults ≥ 35 yr	Mean: 37,456 SD: 21,394 75th: 47,995	RR per 9,392 Age 35–74 yr, lag 0 1.03 (1.00, 1.07)	No copollutant model $r = 0.55 \text{ PM}_{2.5}$

Table 5-43 (Continued): Epidemiologic studies of ultrafine particle (UFP) and respiratory infection.

Study	Exposure Assessment	Outcome Assessment	UFP Concentration Particles/cm ^{3a}	Single Pollutant Effect Estimate 95% CI	UFP Copollutant Model Results and Correlations
†Samoli et al. (2016a)	Barcelona: NC _{5–1,000} nm	Hospital admissions	Means	RR per 10,000	No copollutant model
Barcelona, Spain;	Copenhagen: NC _{6–700} nm	LRI	Barcelona: 19,554	Lag 1	$r = 0.38–0.69$ NO ₂ ,
Copenhagen, Denmark;	Helsinki: NC _{10–100} nm	All ages	Copenhagen: 5,105	0.99 (0.98, 1.01)	0.07–0.67 CO, 0.09–0.57
Helsinki, Finland; Rome,	Rome/Stockholm: NC _{7–3,000} nm		Helsinki: 7,951		PM _{2.5} .
Italy; Stockholm, Sweden			Rome: 34,043		
2001–2011 across cities	One or two monitors per city		Stockholm: 9,128		

CO = carbon monoxide, CI = confidence interval, ED = emergency department, HMO = health maintenance organization, LRI = lower respiratory infection, NC = number concentration, NO₂ = nitrogen dioxide, NR = not reported, PM_{2.5} = particulate matter with a nominal mean aerodynamic diameter ≤2.5 µm, r = correlation coefficient, RR = relative risk, SD = standard deviation, UFP = ultrafine particles, URI = upper respiratory infection.

^aAll data are for 24-hour average.

†Studies published since the 2009 PM ISA.

5.5.5 Combinations of Respiratory-Related Hospital Admissions and Emergency Department (ED) Visits

1 The evidence more consistently links increases in UFP concentration to increases in
2 respiratory-related diseases broadly than to asthma, COPD, or respiratory infections. Recent findings not
3 only add consistency for hospital admissions or ED visits, but they also indicate lung function changes
4 among adults with asthma or COPD. As is observed with asthma exacerbation (Section 5.5.2),
5 distinguishing an association for UFP and respiratory-related diseases independent of NO₂ remains
6 uncertain. As noted previously, studies of respiratory-related diseases examine either all
7 respiratory-related diseases or only a subset, which can complicate the interpretation of results across
8 studies.

9 There is considerable variation across studies in the size fractions examined and, in the fraction,
10 most strongly associated with hospital admissions and ED visits for respiratory-related diseases (Table 5-
11 44). Associations were consistently observed for NC up to 100 nm ([Lanzinger et al., 2016b](#); [Samoli et al., 2016b](#);
12 [Leitte et al., 2011](#); [Andersen et al., 2008b](#); [Halonen et al., 2008](#)). In Beijing, China, associations
13 were observed with UFP NC and SC ([Leitte et al., 2011](#)). Results also are consistent with NC with an
14 upper bound that included larger particles (Table 5-44); however, as detailed in [CHAPTER 1](#), it has been
15 demonstrated that 67–90% of NC represents particles <0.1 µm although the upper bound of the UFP size
16 distribution measured by NC may include larger size particles. In contrast, hospital admissions and ED
17 visits for respiratory-related diseases are inconsistently associated with size fractions with upper bounds
18 less than 50 nm ([Leitte et al., 2011](#); [Halonen et al., 2008](#)).

19 A few recent epidemiologic studies focusing on individuals with a combination of
20 respiratory-related diseases that also examined associations with UFP concentrations provide evidence
21 that supports an association with respiratory-related hospital admissions and ED visits. For adults with
22 asthma and COPD in four European cities (Helsinki, Finland; Athens, Greece; Amsterdam, the
23 Netherlands; Birmingham, U.K.), NC_{total} measured outside the home but not at a monitor in the city was
24 associated with lung function decrements ([de Hartog et al., 2010](#)). Additionally, within the UFIREG
25 study, within Augsburg, Germany, NC_{total} was found to be highly correlated across four traffic and
26 nontraffic sites ($r = 0.77\text{--}0.95$) ([Lanzinger et al., 2016b](#); [Cyrus et al., 2008](#)).

Table 5-44 Epidemiologic studies of UFP and respiratory-related hospital admissions and emergency department (ED) visits.

Study, Location, Years, Age Range	Exposure Assessment	Mean UFP Concentration Particles/cm ^{3a}	Single Pollutant Effect Estimate 95% CI	Copollutant Examination
Hospital admissions				
†Samoli et al. (2016a) Five European cities 2001–2011 All ages	Barcelona: NC _{5–1,000} nm Copenhagen: NC _{6–700} nm Helsinki: NC _{10–100} nm Rome/Stockholm: NC _{7–3,000} nm One or two monitors per city	Barcelona: 19,554 Copenhagen: 5,105 Helsinki: 7,951 Rome: 34,043 Stockholm: 9,128	(ICD9: 466, 480–487; 490–492, 494, 496; 493) Percent increase per 10,000, lag 5 0.43 (–0.58, 1.45)	Correlation (<i>r</i>): 0.38–0.69 NO ₂ , 0.07–0.67 CO, 0.09–0.57 PM _{2.5} Copollutant models with: NO ₂ , CO
†Samoli et al. (2016b) London, U.K. 2011–2012 ≥65 yr	Regional nucleation (nuc) factor 20 nm peak, road traffic factor 30 nm mode, urban background (BG) factor 70 nm peak, long-range transport factor 250 nm mode One monitor	Median Regional nuc: 280 Road traffic: 2,355 Urban BG: 1,893 Long-range transport: 105	(ICD10: J00–J99) RR per IQR, lag 2 Regional nuc: 0.99 (0.98, 1.00) Road traffic: 0.99 (0.97, 1.00) Warm season Urban BG: 1.02 (1.00, 1.04) Long-range: 1.01 (1.00, 1.03)	Correlation (<i>r</i>): NR Copollutant models with: NR
†Lanzinger et al. (2016b) Five European cities (UFIREG) 2011–2014 across cities All ages	NC _{20–100} nm, NC _{20–800} nm One monitor Prague, number of monitors NR in other cities	NC _{20–100} nm, NC _{20–800} nm Augsburg: 5,880, 7,239 Chernivtsi: 5,511, 7,775 Dresden: 4,286, 5,851 Ljubljana: 4,693, 6,750 Prague: 4,197, 5,799	(ICD10: J00–J99) Percent increase per 2,750, Lag 2–5 NC _{20–100} nm: 2.2 (–0.9, 5.3) Percent increase per 3,675, Lag 2–5 NC _{20–800} nm: 3.1 (–0.1, 6.5)	Correlation (<i>r</i>): 0.51 and 0.33 NO ₂ , 0.37 and 0.30 PM _{2.5} (Augsburg and Dresden) Copollutant models with: NO ₂

Table 5-44 (Continued): Epidemiologic studies of ultrafine particle (UFP) and respiratory related hospital admissions and emergency department (ED) visits.

Study, Location, Years, Age Range	Exposure Assessment	Mean UFP Concentration Particles/cm ^{3a}	Single Pollutant Effect Estimate 95% CI	Copollutant Examination
ED visits				
†Leitte et al. (2011)	NC ₁₀₋₃₀ nm, NC ₃₀₋₅₀ nm, NC ₅₀₋₁₀₀ nm, NC _{total}	NC ₁₀₋₃₀ nm: 6,900	(J00-J99)	Correlation (r): With NO ₂ :
Beijing, China		NC ₃₀₋₅₀ nm: 4,900	RR, lag 0	-0.16 NC ₃₋₁₀ nm, -0.09
2004-2006	SC ₅₀₋₁₀₀ nm	NC ₅₀₋₁₀₀ nm: 6,700	NC ₁₀₋₃₀ nm, per 4,300	NC ₁₀₋₃₀ nm, 0.22 NC ₃₀₋₅₀ nm,
All ages	One monitor	UFP (<100 nm): 22,000	0.98 (0.93, 1.04)	0.43 NC ₅₀₋₁₀₀ nm, 0.27
		NC _{total} : 29,000	NC ₃₀₋₅₀ nm, per 2,300	NC _{total} , 0.45 SC ₅₀₋₁₀₀ nm
		SC ₅₀₋₁₀₀ nm: 110	1.03 (0.99, 1.08)	Copollutant models with: NO ₂
			NC ₅₀₋₁₀₀ nm, per 3,600	
			1.03 (0.99, 1.07)	
			UFP, per 11,000	
			1.01 (0.95, 1.07)	
			NC _{total} , per 12,600	
			1.03 (0.98, 1.09)	
			SC ₅₀₋₁₀₀ nm, per 60	
			1.03 (0.99, 1.07)	

CO = carbon monoxide, COPD = chronic obstructive pulmonary disease, CI = confidence interval, LRI = lower respiratory infection, NC = number concentration, NO₂ = nitrogen dioxide, NR = not reported, RR = relative risk, SC = surface concentration, SD = standard deviation, SO₂ = sulfur dioxide, UFIREG = Ultrafine particles—an evidence-based contribution to the development of regional and European environmental and health policy; UFP = ultrafine particles.

^aAll data are for 24-hour average.

†Studies published since the 2009 PM ISA.

Recent results from copollutant models provide additional indication that adjustment for NO₂ or CO has varying effect on UFP associations with respiratory-related diseases. Associations for NC with upper bounds of 100 nm are sometimes attenuated with adjustment for NO₂ (Lanzinger et al., 2016b; Leitte et al., 2011). Other results are for larger sized NC with upper bounds ranging from 290–3,000 nm, with many showing that associations persist with adjustment for NO₂ or CO (Samoli et al., 2016a; Halonen et al., 2009b) and some showing attenuation (Andersen et al., 2008b) (Table 5-44). A wide range of correlations was reported for UFP concentrations with NO₂ and CO ($r = 0.33$ – 0.69 NO₂, 0.07 – 0.69 CO), and the magnitude of correlation does not relate to the copollutant model results.

5.5.6 Respiratory Effects in Healthy Populations

Evidence for a relationship between short-term exposure to UFP and respiratory effects in healthy populations was very limited in the 2009 PM ISA (U.S. EPA, 2009). Epidemiologic studies found an association with wheeze in infants. Controlled human exposure studies found inconsistent evidence for decrements in lung function or pulmonary inflammation following short-term UFP exposure. Animal toxicological studies focused on exposure to mixtures such as woodsmoke and motor vehicle emissions and did not distinguish between the effects of particles and gases in the mixture.

5.5.6.1 Lung Function

5.5.6.1.1 Epidemiologic Studies

While the 2009 PM ISA (U.S. EPA, 2009) did not have a delineated discussion of epidemiologic studies that examined respiratory effects in healthy populations, an association between UFPs and wheeze was reported in a study of infants (Andersen et al., 2008a), in whom wheeze is common and transient. Several recent studies have employed scripted exposures to further inform the relationship between UFPs and respiratory effects in healthy populations. Scripted studies measuring personal ambient UFP exposures are designed to minimize uncertainty in the UFP exposure metric by always measuring UFPs at the site of exposure, ensuring exposure to sources of UFPs, such as traffic, and measuring outcomes at well-defined lags after exposure. A limitation of recent scripted exposure studies is that outcome assessment is only performed up to 6 hours after exposure, such that scripted studies do not inform understanding of the persistence of effects. There are recent epidemiologic studies in populations that include a mix of healthy participants and participants with pre-existing respiratory and/or cardiovascular disease, some of which indicate UFP-associated increases in respiratory effects. However, these studies are not evaluated in this section, as it is not known whether the results apply to the healthy portion of the population or are instead driven solely by an association in individuals with pre-existing respiratory conditions.

1 Respiratory effects were evaluated in recent panel studies of scripted exposures in high or low
2 traffic areas, commute routes, or participants assigned to spend time at varying distance to a steel plant.,
3 Exposures ranged from 1 to 8 hours and the nature of exposure varied among the traffic studies, including
4 cycling on roadways ([Weichenthal et al., 2011](#); [Zuurbier et al., 2011b](#)), riding in a car or bus on roadways
5 ([Zuurbier et al., 2011b](#)), and exercising near high and low traffic areas on stationary bicycles ([Matt et al.,](#)
6 [2016](#); [Kubesch et al., 2015](#); [Steenhof et al., 2013](#); [Strak et al., 2012](#)). In addition to traffic studies, [Dales et](#)
7 [al. \(2013\)](#) randomly assigned participants to spend alternating weeks in a neighborhood within 1 km of a
8 steel plant, and at a neighboring college campus, 4.5 km from the plant. In addition to varying study
9 designs, UFP concentration metrics also varied across studies. Most studies examined NC, with a few
10 specifying sampling in the 10–1,000 nm range ([Matt et al., 2016](#); [Kubesch et al., 2015](#); [Dales et al.,](#)
11 [2013](#)).

12 In recent studies, increases in personal ambient UFP exposure were inconsistently associated with
13 decreases in lung function and increases in markers of pulmonary inflammation in healthy adults in recent
14 studies. Some studies provided evidence of transient respiratory effects associated with UFP exposure.
15 [Strak et al. \(2012\)](#) reported decreases in FVC and FEV₁, and increases in eNO immediately after
16 exposure, but not 6 or 18 hours later. Similarly, [Matt et al. \(2016\)](#) observed UFP-related FEV₁ decrements
17 immediately after exposure that were positive 7-hour post exposure. Other studies observed associations
18 with several lung function metrics, including FEV₁, FEV₁/FVC, FEF_{25–75%}, total lung capacity (TLC), and
19 residual volume (RV) ([Dales et al., 2013](#)) immediately after exposure, and PEF 2 and 6 hours after
20 exposure ([Zuurbier et al., 2011b](#)). Notably, many studies that reported some evidence of associations had
21 inconsistent results across an array of lung function metrics ([Matt et al., 2016](#); [Strak et al., 2012](#); [Zuurbier](#)
22 [et al., 2011b](#)). Similarly, some studies reported UFP associations with lung function and eNO, but not
23 other subclinical pulmonary effects, including nasal lavage levels of the proinflammatory cytokine IL-6
24 ([Steenhof et al., 2013](#); [Strak et al., 2012](#)) or plasma CC16 levels ([Zuurbier et al., 2011a](#)), an indicator of
25 decreased lung epithelial barrier function. Additional studies did not observe any associations between
26 UFP concentrations and lung function or pulmonary inflammation in healthy populations up to 7 hours
27 after exposure ([Kubesch et al., 2015](#); [Weichenthal et al., 2011](#); [Strak et al., 2010](#)). While respiratory
28 symptoms are frequently studied in populations with pre-existing respiratory conditions, such as asthma
29 or COPD, the outcome is less often examined in healthy populations. As such, no recent studies of UFP
30 exposure evaluate respiratory symptoms or medication use in healthy populations.

31 In addition to major uncertainties regarding the spatial variability in UFP and the various size
32 fractions and concentration metrics used as UFP exposure surrogates, the ability to attribute inconsistently
33 observed associations to UFP exposure in the presence of moderately-to-highly correlated traffic-related
34 copollutants ($r = 0.50–0.70$) remains limited. Only [Strak et al. \(2012\)](#) examined models with these
35 copollutants. The authors reported that UFP associations observed immediately after exposure persisted in
36 copollutant models including EC, Fe, Cu, NO₂, or NO_x, but results may be unreliable for models with
37 moderately-to-highly correlated pollutants.

5.5.6.1.2 Controlled Human Exposure Studies

1 The 2009 PM ISA (U.S. EPA, 2009) reported evidence of small decrements in lung function
2 following short-term UFP CAPs exposure in healthy humans in one study (Gong et al., 2008) but not
3 another (Samet et al., 2009). In contrast, an increase in BALF IL-8 was found in Samet et al. (2009), but
4 no evidence of pulmonary inflammation was found in Gong et al. (2008).

5.5.6.1.3 Animal Toxicological Studies

5 The 2009 PM ISA (U.S. EPA, 2009) did not report any animal toxicological studies investigating
6 the effects of short-term exposure to UFP on pulmonary function. Animal toxicological studies
7 investigating the effects of short-term exposure to UFP-containing mixtures on subclinical effects did not
8 distinguish between effects due to particles or gases in the mixture.

9 Two recent studies examined this endpoint. In one study, Sprague Dawley rats were exposed for
10 6 hours to filtered and unfiltered GE (count median diameter of 15–20 nm, mass median diameter of
11 approximately 150 nm) (Seagrave et al., 2008). Neither filtered nor unfiltered GE exposure caused any
12 change in breathing frequency, tidal volume, minute volume, or Penh. In the other study, Amatullah et al.
13 (2012) found that a 4-hour exposure of BALB/c mice to Toronto near-UFP CAPs had no effect on
14 pulmonary function. Additional study details for these and other recent animal toxicological studies are
15 found in Table 5-45.

Table 5-45 Study-specific details from animal toxicological studies of short-term exposure to UFP and respiratory effects in healthy animals.

Study/Study Population	Pollutant	Exposure	Endpoints
<u>Aztatzi-Aguilar et al. (2015)</u> Species: Rat Sex: Male Strain: Sprague Dawley	UFP CAPs Mexico City Particle size: (UF) Ultrafine PM _{0.2} Control: Filtered air	Route: Inhalation Dose/Concentration: Ultrafine PM _{0.2} 107 µg/m ³ Duration: Acute 5 h/day, 3 days Time to analysis: 24 h	Gene and protein expression in lung tissue <ul style="list-style-type: none"> • IL-6 • Components of kallikrein-kinin endocrine system and RAS • Heme oxygenase-1
<u>Cheng et al. (2016)</u> Species: Mouse Strain: C57Bl/6J Sex: Male Age: 3 mo	Re-aerosolized collected ambient PM near a Los Angeles freeway Particle sizes: Ultrafine PM < 180 nm, median 60.6 nm Control: Reaerosolized extracts of sham filters	Route: Whole-body inhalation Dose/concentration: 343 µg/m ³ Duration of exposure: 5 h/day, 3 days/week for 5, 20 and 45 h over 3 weeks	Immunohistochemistry of nasal epithelium and brain tissue <ul style="list-style-type: none"> • Oxidative stress markers • Macrophage activation marker
<u>Seagrave et al. (2008)</u> Species: Rat Strain: Sprague-Darley Sex: Male Age/Weight: 8–10 weeks, 250–300 g	Gasoline engine exhaust (GE) Filtered GE Particle Size: GE MMD 150 nm	Route: Whole-body inhalation Dose/Concentration: GE filtered 2.4 µg/m ³ GE 59 µg/m ³ Duration of exposure: 6 h Coexposure: Combustion vapors	Pulmonary function <ul style="list-style-type: none"> • Breathing frequency • Tidal volume • Minute volume • Penh
<u>Tyler et al. (2016)</u> Species: Mouse Strain: C57BL/6 and ApoE knockout Age/Weight: 6–8 weeks	Motor vehicle exhaust (DE and GE) passed through a denuder to generate UFP Particle size: 147.1 nm ± 1.3 nm Control: Filtered air	Route: Whole-body inhalation Dose/Concentration: 371.3 ± 15.6 µg/m ³ Duration: 6 h	BALF cells and cytokines Particle uptake in bronchial macrophages

ApoE = apolipoprotein E; DE = diesel exhaust; GE = gasoline exhaust; MMD = mass median diameter; Penh = enhanced pause.

Pulmonary Oxidative Stress

1 The 2009 PM ISA ([U.S. EPA, 2009](#)) did not report any animal toxicological studies investigating
2 the effects of short-term UFP exposure on pulmonary oxidative stress. Two recent studies examined this
3 endpoint. [Seagrave et al. \(2008\)](#) exposed rats to GE (count median diameter 15–20 nm, mass median
4 diameter 150 nm) and found increased lung tissue chemiluminescence that was not present when GE was
5 filtered, indicating that the particulate fraction had a role in the oxidative stress response. Recently,

oxidative stress in olfactory epithelium, as well as olfactory bulb and other brain regions, was examined in mice exposed to resuspended urban UFP (Cheng et al., 2016) (see Section 8.5.2). A single 5-hour exposure to UFP resulted in enhanced markers of oxidative stress in olfactory epithelium, but not olfactory bulb, cerebellum, or cerebral cortex. Multiple exposures over 3 weeks also increased oxidative stress markers in olfactory epithelium, as well as decreased levels of a protein expressed by olfactory sensory nerves, and increased levels of apoptosis-related proteins.

Pulmonary Inflammation

The 2009 PM ISA (U.S. EPA, 2009) did not report any animal toxicological studies investigating the effects of short-term UFP exposure on pulmonary inflammation. Several recent studies examined this endpoint. No effects were observed in terms of BALF inflammatory cells in response to a 4-hour exposure of BALB/c mice to Toronto UFP CAPs (Amatullah et al., 2012) or in response to a 6-hour exposure of C57BL/6 mice to UFP generated from motor vehicle exhaust (Tyler et al., 2016), despite effects observed in the hippocampus of the latter study (see Section 8.5.2). However, inflammation was observed in two other studies measuring effects in lung tissue. Cheng et al. (2016) found inflammatory responses in olfactory epithelium, as well as olfactory bulb and other brain regions, in C57BL/6J mice exposed to resuspended urban UFP (Section 8.5.2). The number of Iba1 positive-macrophages, an indicator of inflammation, increased in olfactory epithelial turbinates and in the olfactory bulb after 5-hours of exposure to UFP ($p < 0.05$). In addition, Aztatzi-Aguilar et al. (2015) found increased levels of IL-6 in lung tissue in Sprague Dawley rats exposed to UFP CAPs in Mexico City for several days ($p < 0.05$). Aztatzi-Aguilar et al. (2015) also found that short-term UFP CAPs exposure had several effects on the two counterbalancing endocrine systems—the RAS and the kallikrein-kinin system in the lung ($p < 0.05$). These effects included upregulation of genes encoding angiotensin 1 receptor and angiotensin converting enzyme and reduced levels of reduced angiotensin 1 receptor protein. Levels of angiotensin converting enzyme protein and angiotensin 2 receptor mRNA were not impacted. The RAS plays an important role in pulmonary and systemic vasculature, with binding of angiotensin to the angiotensin 1 receptor mediating vasoconstriction and oxidative stress. In addition, short-term UFP CAPs exposure resulted in upregulation of the gene encoding kallikrein-1 ($p < 0.05$). Kallikrein-1 is a serine protease enzyme required to produce kinin peptides, which are necessary to activate bradykinin receptors. Bradykinin receptors are involved in the regulation of nitric oxide which mediates vasodilation.

5.5.6.2 Summary of Respiratory Effects in Healthy Populations

Evidence linking short-term UFP exposure and respiratory effects in healthy populations is inconsistent or minimal in epidemiologic studies and controlled human exposure studies. Animal toxicological studies found pulmonary oxidative stress following short-term UFP exposure, but inconsistent evidence of pulmonary inflammation and no evidence of changes in lung function.

5.5.7 Respiratory Effects in Populations with Cardiovascular Disease

As described in the 2009 PM ISA (U.S. EPA, 2009), Kooter et al. (2006) found that a multiday exposure of SH rats to UFP-enriched CAPs in the Netherlands decreased CC16 in BALF. CC16 is a secretory product of nonciliated bronchiolar Club cells and is thought to contribute to control of inflammation. Recently, Tyler et al. (2016) exposed C57BL/7 and ApoE knockout mice for 6-hour to UFP generated from motor vehicle exhaust. No increases in BALF inflammatory cells were observed. However, increases in TNF- α levels in BALF and particle uptake into bronchial macrophages were found in ApoE knockout ($p < 0.001$) but not in C57BL/6 mice. Effects were also seen in the hippocampus (Section 8.5.2). Additional study details are presented in Table 5-45.

5.5.8 Respiratory Mortality

In the 2009 PM ISA (U.S. EPA, 2009), no studies specifically examined associations between short-term UFP exposure and respiratory mortality. Although recent studies examine the relationship between short-term UFP exposure and respiratory mortality, the total body of evidence remains small, as detailed in CHAPTER 11 (Section 11.4.1). Across studies that examined the UFP—respiratory mortality relationship, there is inconsistency in the particle size distribution that was used to represent UFP exposures with some studies measuring NC, while other studies measured NC with the upper end of the size distribution ranging from 100—3,000 nm. This disparity in the measurement of UFPs between studies complicates the overall interpretation of results.

The assessment of the relationship between short-term UFP exposure and respiratory mortality is limited to studies conducted in Europe (Stafoggia et al., 2017; Lanzinger et al., 2016a; Samoli et al., 2016b) and China (Leitte et al., 2012). Across studies of respiratory mortality, NC was used to examine associations with respiratory mortality. Both Lanzinger et al. (2016a), in a study of five central European cities as part of the UFIREG project, and Leitte et al. (2012), in Beijing, China, reported generally positive associations that were imprecise across each of the UFP size distributions examined (Table 11-9, UFP studies in mortality chapter), while Samoli et al. (2016b) did not report any evidence of an association with respiratory mortality. Although there is some evidence of a positive association between short-term UFP exposure and respiratory mortality, within each study only a single monitor was used to estimate exposure to UFPs (Table 11-9, UFP studies in mortality chapter). As detailed in CHAPTER 2 (Section 2.5.1.1.5, Section 2.5.1.2.4, and Section 2.5.2.2.3), the use of a single monitor does not adequately account for the spatial and temporal variability in UFP concentrations as well as the change in the particle size distribution that changes with distance from source.

5.5.9 Summary and Causality Determination

1 A limited number of studies examining short-term exposure to UFPs and respiratory effects were
2 reported in the 2009 PM ISA (U.S. EPA, 2009), which concluded that the relationship between short-term
3 exposure to UFP and respiratory effects is “suggestive of a causal relationship”. This conclusion was
4 based on epidemiologic evidence indicating associations with combined respiratory-related diseases,
5 respiratory infection, and asthma exacerbation. In addition, personal ambient UFP exposure from time
6 spent in high- and low-traffic areas were associated with lung function decrements in adults with asthma.
7 The few available experimental studies provided limited coherence with epidemiologic findings for
8 asthma exacerbation. Recent studies add to this evidence base and support epidemiologic evidence for
9 asthma exacerbation and combined respiratory-related diseases but do not rule out chance, confounding,
10 and other biases. Several animal toxicological studies showing effects related to allergic asthma provide
11 biological plausibility. The evidence characterizing the relationship between short-term exposure to UFP
12 and effects on the respiratory is detailed below (Table 5-46), using the framework for causality
13 determinations described in the Preamble to the ISAs (U.S. EPA, 2015).

14 For asthma exacerbation, there is some epidemiologic evidence that is not entirely consistent.
15 Associations persisted in one epidemiologic study with adjustment for NO₂, but not in another. Additional
16 supporting evidence, showing decrements in lung function and enhancement of allergic inflammation and
17 other allergic responses, is provided by a controlled human exposure study in adults with asthma and by
18 animal toxicological studies in an animal model of allergic airway disease. For combined
19 respiratory-related diseases, recent findings add consistency for hospital admissions and ED visits and
20 indicate lung function changes among adults with asthma or COPD. Uncertainty remains regarding the
21 representativeness of UFP concentrations as a surrogate for exposure and for copollutant confounding,
22 which limits inference about an independent effect of UFP. Additionally, there remains limited
23 information on the spatial and temporal variability of UFP concentrations (Section 2.4.3.1). **Overall, the**
24 **evidence is suggestive of, but not sufficient to infer, a causal relationship between short-term UFP**
25 **exposure and respiratory effects.**

Table 5-46 Summary of evidence for that is suggestive of, but not sufficient to infer, a causal relationship between short-term UFP exposure and respiratory effects.

Rationale for Causality Determination ^a	Key Evidence ^b	Key References ^b	UFP Concentrations Associated with Effects ^c
Asthma exacerbation and combined respiratory-related diseases			
Evidence from multiple, high quality epidemiology studies at relevant UFP concentrations is generally consistent, but limited	Increases in asthma-related hospital admissions, ED visits, and physician visits in children and all ages combined.	Samoli et al. (2016a) Iskandar et al. (2012) Evans et al. (2014)	
	Increases in combined respiratory-related diseases observed in single-city and multicity studies.	Section 5.5.5	
Uncertainty regarding confounding by copollutants	Potential copollutant confounding for asthma-related hospital admissions and lung function is examined in a few studies, with some evidence that associations remain robust in models with gaseous pollutants.	Andersen et al. (2008b) McCreanor et al. (2007) Samoli et al. (2016a) Halonen et al. (2009b)	
Limited coherence in epidemiologic studies across the continuum of effects	Increases in respiratory symptoms, pulmonary inflammation and lung function decrements observed in a limited number of panel studies in adults with asthma provide limited support for asthma exacerbation in children.	Mar et al. (2004) von Klot et al. (2002) McCreanor et al. (2007) Mirabelli et al. (2015)	
Uncertainty regarding exposure measurement error	Most studies relied on one monitor to measure UFPs, which is inadequate based on limited data demonstrating both that there is greater spatial variability in UFPs (i.e., NC) and that the particle size distribution changes with distance from source. Additionally, there is limited information on the temporal variability in UFP concentrations.	Section 2.4.3.1	
Uncertainty regarding exposure metric and UFP size fraction	Inconsistency in the UFP metric used (i.e., NC, SC, and MC) and UFP size fraction examined complicating interpretation of results across studies.	Table 5-40 Table 5-42 Table 5-43 Table 5-44 Section 5.5.8	

Table 5-46 (Continued): Summary of evidence for that is suggestive of, but not sufficient to infer, a causal relationship between short term ultrafine particle (UFP) exposure and respiratory effects.

Rationale for Causality Determination ^a	Key Evidence ^b	Key References ^b	UFP Concentrations Associated with Effects ^c
Limited evidence from controlled human exposure studies	In adults with asthma, decreases in pulmonary function are observed.	Gong et al. (2008)	100 µg/m ³
Limited evidence from toxicological studies at relevant concentrations	Enhancement of allergic inflammation and other allergic responses is observed in animal model of allergic airway disease.	Section 5.5.2.3 Li et al. (2009)	101 µg/m ³
Biological plausibility for allergic asthma	Evidence from animal toxicological studies provides biological plausibility for epidemiologic findings of allergic asthma, the most common phenotype in children.	Section 5.5.1 Section 5.5.2.3	
Respiratory effects in healthy populations			
Some evidence from toxicological studies at relevant concentrations	Pulmonary function was not affected. Inconsistent results were found for pulmonary inflammation, while some evidence was found for oxidative stress and changes in the RAS.	Section 5.5.6.1.3	59–793 µg/m ³

^aBased on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble to the ISAs ([U.S. EPA, 2015](#)).

^bDescribes the key evidence and references, supporting or contradicting, contributing most heavily to causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where full body of evidence is described.

^cDescribes the UFP concentrations and metric (i.e., number concentration [NC], surface area concentration [SC], mass concentration [MC]) with which the evidence is substantiated.

5.6 Long-Term UFP Exposure and Respiratory Effects

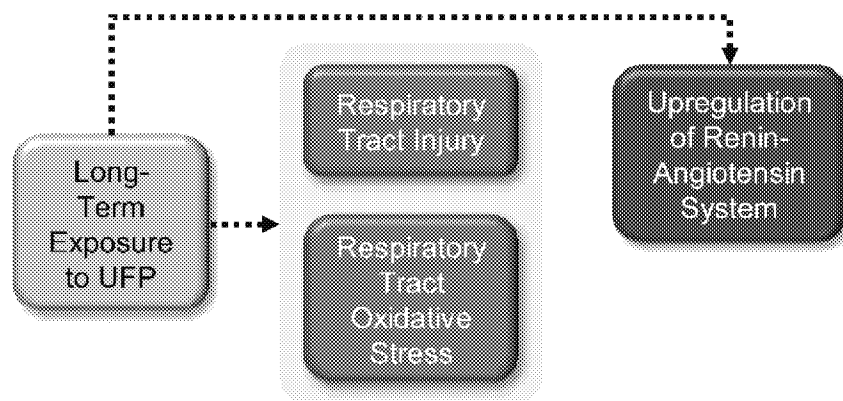
The 2009 PM ISA concluded that the evidence was inadequate to assess the relationship between long-term exposure to UFP and respiratory effects ([U.S. EPA, 2009](#)). At that time, there were no epidemiologic studies available to address this relationship. Animal toxicological studies found that long-term exposure to UFP CAPs had no effect, while long-term exposure to GE and DE altered respiratory-related endpoints. Studies with DE did not determine whether the effects were due to the particulate or gaseous part of the mixture. However, the effects of the GE were attributable to particulate matter. Recent studies consist of one epidemiologic study that examines the association between long-term exposure to UFP and respiratory outcomes and a small number of recent animal toxicological studies that provide evidence for respiratory effects.

5.6.1 Biological Plausibility

1 Due to a paucity of data, it is not possible to describe biological pathways that potentially
2 underlie respiratory effects resulting from long-term exposure to UFP. Figure 5-50 graphically depicts the
3 upstream events that may lead to downstream events observed in the single epidemiologic study. This
4 discussion of “how” long-term exposure to UFP may lead to respiratory effects contributes to an
5 understanding of the biological plausibility of epidemiologic results evaluated later in Section 5.6.

6 Once UFP deposits in the respiratory tract, it may be retained, cleared, or solubilized
7 (see CHAPTER 4). UFP and its soluble components may interact with cells in the respiratory tract, such
8 as epithelial cells, inflammatory cells, and sensory nerve cells. One way in which this may occur is
9 through reduction-oxidative (redox) reactions. As discussed in Section 2.3.3, PM may generate ROS and
10 this capacity is termed “oxidative potential.” Furthermore, cells in the respiratory tract may respond to the
11 presence of PM by generating ROS. Further discussion of these redox reactions, which may contribute to
12 oxidative stress, is found in Section 5.1.1 of the 2009 PM ISA (U.S. EPA, 2009). In addition, poorly
13 soluble particles may translocate to the interstitial space beneath the respiratory epithelium and
14 accumulate in the lymph nodes (see CHAPTER 4). Immune system responses due to the presence of
15 particles in the interstitial space may contribute to respiratory health effects.

16 Although all size fractions of PM may contribute to oxidative stress, UFPs may contribute
17 disproportionately more as a function of their mass due to their large surface/volume ratio. The relative
18 enrichment of redox active surface components, such as metals and organics, per unit mass may translate
19 to a relatively greater oxidative potential of UFPs compared with larger particles with similar surface
20 components. In addition, the greater surface per unit volume may deliver relatively more adsorbed soluble
21 components to cells. These components may undergo intra-cellular redox cycling following cellular
22 uptake. Furthermore, per unit mass, UFPs may have more opportunity to interact with cell surfaces due to
23 their greater surface area and their greater particle number compared with larger PM. These interactions
24 with cell surfaces may lead to ROS generation, as described in Section 5.1.1 of the 2009 PM ISA (U.S.
25 EPA, 2009). Recent studies have also demonstrated that UFPs have the capacity to cross cellular
26 membranes by nonendocytotic mechanisms involving adhesive interactions and diffusion, as described in
27 CHAPTER 4. This may allow UFPs to interact with or penetrate intra-cellular organelles.



Note: The boxes above represent the effects for which there is experimental or epidemiologic evidence, and the dotted arrows indicate a proposed relationship between those effects. Progression of effects is depicted from left to right and color-coded (gray, exposure; green, initial event; blue, intermediate event; orange, apical event). Here, apical events generally reflect results of epidemiologic studies, which often observe effects at the population level. Epidemiologic evidence may also contribute to upstream boxes. When there are gaps in the evidence, there are complementary gaps in the figure and the accompanying text below.

Figure 5-50 Potential biological pathways for respiratory effects following long-term UFP exposure.

Evidence that long-term exposure to UFP may affect the respiratory tract is provided by a limited number of experimental studies. While markers of injury and oxidative stress were increased (Zhang et al., 2012; Reed et al., 2008), no inflammatory changes were observed (Tyler et al., 2016; Aztatzi-Aguilar et al., 2015; Araujo et al., 2008; Reed et al., 2008). In Tanaka et al. (2013a), the enhancement of allergic responses seen following long-term exposure to UFP-enriched DE was not attributable to particulate components, suggesting a role for combustion gases in mediating the response. Similarly, the presence of 8-OH deoxy-guanosine observed in lung tissue was likely due to combustion gases. Upregulation of the RAS, as indicated by an increase in mRNA and protein levels of angiotensin receptor Type 1, was observed in the lung (Aztatzi-Aguilar et al., 2015). Angiotensin receptor Type 1 mediates the effects of angiotensin II, which is a potent vasoconstrictor and mediator in the vasculature. The SNS and the RAS are known to interact in a positive feedback fashion (Section 8.1.2) with important ramifications in the cardiovascular system. However, it is not known whether SNS activation or some other mechanism mediated the changes in the RAS observed in the respiratory tract in this study. The upstream events presented here may provide biological plausibility for epidemiologic evidence of respiratory health effects and will be used to inform a causality determination, which is discussed later in the chapter (Section 5.4.9).

5.6.2 Development of Asthma

1 The 2009 PM ISA (U.S. EPA, 2009) did not report any studies evaluating allergic responses
2 resulting from long-term exposure to UFP. Recently, Tanaka et al. (2013a) evaluated the enhancement of
3 allergic responses by exposure to UFP-enriched DE. ICR mice were exposed to two concentrations of
4 diluted DE and to particle-depleted diesel exhaust (0DE) for 8 weeks. Concentrations of gaseous
5 components of DE were similar in the high DE and 0DE atmospheres (3.3 ppm CO, 1.4 ppm NO_x, and
6 0.51 ppm NO₂), but the low DE had approximately 1/3 of these concentrations (1.2, 0.41, and 0.15,
7 respectively). Mice were sensitized and challenged with OVA administered by intra-tracheal instillation
8 during the 8-week inhalation exposure. Mice exposed to filtered air and OVA had a modest increase in
9 airway eosinophils that was enhanced by exposure to low and high DE in a dose-dependent fashion
10 ($p < 0.05$ compared with OVA controls). This response was not dependent on the particulate part of the
11 aerosol, since numbers of eosinophils in allergic animals exposed to 0DE, which was depleted of
12 particles, were similar in the high DE group. Furthermore, increases in IL-5, IL-13, eotaxin, and
13 myeloperoxidase protein in lung tissue reached similar levels in allergic mice exposed to either high DE
14 or 0DE ($p < 0.05$ compared with OVA controls). Interestingly, only the allergic mice exposed to the
15 particle-depleted 0DE had increases in lung tissue IL-4, IL-17 α , IL-1 β , lipid peroxidase, and serum IgE
16 ($p < 0.05$ compared with OVA controls). Results from this study indicate a critical role for the
17 combustion gases in DE-associated enhancement of allergic responses. Companion studies also detected
18 the presence of 8-OH deoxy-guanosine in lung tissue in high DE and particle-depleted 0DE allergic mice
19 (Tanaka et al., 2013b). Additional study details are found in Table 5-47.

Table 5-47 Study-specific details from animal toxicological studies of long-term UFP exposure and allergic responses.

Study/Study Population	Pollutant	Exposure	Endpoints
<u>Tanaka et al. (2013a)</u> Species: Mouse Sex: Female Strain: ICR Age/Weight: 6 weeks	Diesel engine exhaust Low DE = 36 µg/m ³ High DE = 169 µg/m ³ Particle size: 26–27 nm in low and high DE	Route: Whole-body inhalation Dose/Concentration: 5 h/day, 5 days/week for 8 weeks OVA intra-tracheal every other week (5 total) Time to analysis: 24 h after last instillation	BALF cells BALF cytokines Serum IgE
<u>Tanaka et al. (2013b)</u> Species: Mouse Sex: Female Strain: ICR Age/Weight: 6 weeks	Diesel engine exhaust Low DE = 36 µg/m ³ High DE = 169 µg/m ³ Particle size: 26–27 nm in low and high DE	Route: Whole-body inhalation Dose/Concentration: 5 h/day, 5 days/week for 8 weeks OVA intra-tracheal every other week (5 total) Time to analysis: 24 h after last instillation	Oxidative stress • -Lung 8-OH deoxy guanosine levels

BALF = bronchoalveolar lavage fluid; DE = diesel exhaust; IgE = Immunoglobulin E; OVA = ovalbumin.

5.6.3 Subclinical Effects in Healthy Populations and Populations with Cardiovascular Disease

Animal toxicological studies provide evidence for subclinical effects potentially underlying the development of respiratory disease in healthy populations and in populations with cardiovascular disease. The 2009 PM ISA (U.S. EPA, 2009) reported several studies that evaluated the effects of long-term exposure to UFP on subclinical effects. Reed et al. (2008) exposed F344 rats for 6 months to GE containing UFP (count median diameter 15–20 nm, MMD 150 nm). LDH was increased in BALF of rats, but no inflammatory or histopathologic changes were found except for the accumulation of PM-containing macrophages. However, hypermethylation of lung DNA was observed. The significance of DNA methylation in terms of respiratory health is unclear, although it is known that altered patterns of DNA methylation can affect gene expression and are sometimes associated with altered immune responses and/or the development of cancer. The LDH and hypermethylation responses were prevented by addition of a particle filter, indicating that the particulate portion of the GE mixture played a role in the response. In a study in ApoE knockout mice exposed to UFP CAPs for 40 days, Araujo et al. (2008) found no increase in BALF inflammatory cells exposed to UFP CAPs for 40 days.

Several recent studies have become available since the 2009 PM ISA that examine the effects of long-term UFP exposure on pulmonary oxidative stress and inflammation. Zhang et al. (2012) collected ambient UFP near a Los Angeles freeway. Exposure of C57BL/6J mice to the re-aerosolized UFP for

1 10 weeks resulted in increases in mRNA and protein levels of heme oxygenase-1, NADPH quinone
2 oxidoreductase 1, γ -glutamyl cysteine ligase catalytic subunit, and γ -glutamyl cysteine synthetase
3 modifier subunit in the lung ($p < 0.05$). These are Phase II regulated detoxifying enzymes and are
4 important in defense against oxidative stress. Young mice (3 months) had a more robust increase in gene
5 expression and protein levels than older mice (18 months). [Zhang et al. \(2012\)](#) also found evidence of
6 upregulation of Phase II enzymes in specific brain regions (Section 8.6.3) and the liver. In contrast,
7 [Aztatzi-Aguilar et al. \(2015\)](#) found decreased lung tissue heme oxygenase-1 activity in Sprague-Dawley
8 rats following 8-weeks exposure to Mexico City UFP CAPs ($p < 0.05$) and no change in γ -glutamyl
9 cysteine ligase catalytic subunit was observed. [Aztatzi-Aguilar et al. \(2015\)](#) also found decreased protein
10 levels of IL-6 in lung tissue ($p < 0.05$). Further, [Tyler et al. \(2016\)](#) exposed C57BL/7 and ApoE-knockout
11 mice to UFP generated from motor vehicle exhaust. A 30-day exposure resulted in no increase in
12 inflammatory cells or cytokines in the BALF. Particle uptake into bronchial macrophages was increased
13 in both C57BL/6 and ApoE knockout mice ($p < 0.05$). Effects were also seen in the hippocampus
14 (Section 8.6.3). [Aztatzi-Aguilar et al. \(2015\)](#) found that long-term UFP CAPs exposure had several effects
15 on the RAS, including induced lung expression of the angiotensin 1 receptor gene, and increased
16 angiotensin 1 receptor protein levels ($p < 0.05$). Protein levels and mRNA of angiotensin converting
17 enzyme were not impacted. Components of the RAS play an important role in the pulmonary circulation.
18 Overall, older and recent studies provide some limited evidence for pulmonary injury, DNA
19 hypermethylation, and changes in the RAS, inconsistent evidence for pulmonary oxidative stress and no
20 evidence for pulmonary inflammation. Additional study details for these recent animal toxicological
21 studies are found in Table 5-48.

Table 5-48 Study-specific details from animal toxicological studies of long-term UFP exposure and respiratory effects in healthy animals.

Study/Study Population	Pollutant	Exposure	Endpoints
<u>Aztatzi-Aguilar et al. (2015)</u> Species: Rat Sex: Male Strain: Sprague Dawley	UFP CAPs Mexico City Particle size: Ultrafine PM _{0.2} Control: Filtered air	Route: Inhalation Dose/Concentration: Ultrafine PM _{0.2} 107 µg/m ³ Duration: Subchronic 5 h/day, 4 days/week, 8 weeks Time to analysis: 24 h	Gene and protein expression in lung tissue <ul style="list-style-type: none"> • IL-6 • Components of kallikrein-kinin endocrine system and RAS • Heme oxygenase-1
<u>Reed et al. (2008)</u> Species: Rat Sex: Male and Female Strain: F344 Age/Weight:	DE and filtered DE Particle size: MMAD 150 nm	Route: Whole-body Inhalation Dose/Concentration: 3 concentrations, H 59 µg/m ³ , M 30 µg/m ³ , L 6.6 µg/m ³ , high filtered 2 µg/m ³ Duration: 6 h/day for 7 days/week, 3 days (1 week), 6 mo Coexposure: Combustion products	Lung Injury <ul style="list-style-type: none"> • -BALF LDH Lung DNA Alteration—Hypermethylation
<u>Tyler et al. (2016)</u> Species: Mouse Strain: C57BL/6 and ApoE knockout Age/Weight: 6–8 weeks	Motor vehicle exhaust (DE and GE) passed through a denuder to generate UFP Particle size: 147.1 nm ± 1.3 nm Control: Filtered air	Route: Whole-body inhalation Dose/Concentration: 371.3 ± 15.6 µg/m ³ Duration: 6 h/day for 30 days	BALF cells and cytokines Particle uptake in bronchial macrophages
<u>Zhang et al. (2012)</u> Species: Mouse Strain: C57BL/6J Sex: Male Age: 3 mo, 18 mo	Reaerosolized collected ambient PM near a freeway Particle size: Ultrafine PM < 200 nm	Route: Whole-body inhalation Dose/concentration: 200–400 µg/m ³ Duration of exposure: 5 h/day, 3 days/week for 10 weeks	Oxidative Stress Markers—Lung GCLC and GCLM mRNA and protein

ApoE = apolipoprotein E; BALF = bronchoalveolar lavage fluid; DNA = deoxyribonucleic acid; DE = diesel exhaust; GCLC = glutamate cysteine ligase catalytic subunit; GCLM = glutamate cysteine ligase modifier subunit; H = high; IL-6 = interleukin 6; L = low; M = medium; MMAD = mass median aerodynamic diameter; LDH = lactate dehydrogenase; Mrna = messenger ribonucleic acid; RAS = renin-angiotensin system.

5.6.4 Respiratory Mortality

Overall, the literature base for long-term UFP exposure and respiratory mortality remains very small, with one study (Ostro et al., 2015) reporting results for UFP mass concentration. The authors examined the association between UFP (<0.1 µm) mass concentrations and respiratory mortality among

women in the California Teachers Cohort using a CTM to predict UFP concentrations with a 4-km spatial resolution and observed an association near the null value.

5.6.5 Summary and Causality Determination

Based on limited evidence from animal toxicological studies and a lack of epidemiologic studies, the 2009 PM ISA (U.S. EPA, 2009) concluded that evidence was inadequate to assess the relationship between long-term exposure to UFP and respiratory effects. Since then, only a few new studies have become available. The evidence characterizing the relationship between long-term exposure to PM_{10-2.5} and respiratory effects is detailed below (Table 5-49), using the framework for causality determination described in the Preamble to the ISAs (U.S. EPA, 2015). Currently, there is limited epidemiologic evidence for respiratory mortality. But uncertainty regarding copollutant confounding and exposure measurement error results in an inability to rule out chance and confounding. A few animal toxicological studies provide evidence of effects resulting from long-term exposure to UFP. **Overall, the evidence is inadequate to infer the presence or absence of a causal relationship between long-term UFP exposure and respiratory effects.**

Table 5-49 Summary of evidence that is inadequate to infer the presence or absence of a causal relationship between long-term UFP exposure and respiratory effects.

Rationale for Causality Determination ^a	Key Evidence ^b	Key References ^b	UFP Concentrations Associated with Effects ^c
Limited epidemiologic evidence does not support a relationship	No association was observed with UFP mass concentrations in a single study of respiratory mortality from the California Teachers Study cohort.	Ostro et al. (2015)	UF mass concentration: 1.29
Uncertainty regarding confounding by copollutants and exposure measurement error	Uncertainties are not addressed.	Ostro et al. (2015)	
Some evidence for respiratory effects from toxicological studies at relevant concentrations	Results show injury, oxidative stress, DNA hypermethylation, and changes in the RAS, but no pulmonary inflammation.	Section 0	59–400 µg/m ³

^aBased on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble to the ISAs ([U.S. EPA, 2015](#)).

^bDescribes the key evidence and references, supporting or contradicting, contributing most heavily to causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where full body of evidence is described.

^cDescribes the UFP concentrations and metric (i.e., number concentration [NC], surface area concentration [SC], mass concentration [MC]) with which the evidence is substantiated.

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CHAPTER 6 CARDIOVASCULAR EFFECTS

Summary of Causality Determinations for Short- and Long-Term Particulate Matter (PM) Exposure and Cardiovascular Effects

This chapter characterizes the scientific evidence that supports causality determinations for short- and long-term PM exposure and cardiovascular effects. The types of studies evaluated within this chapter are consistent with the overall scope of the ISA as detailed in the Preface (see Section 11P.3.1). In assessing the overall evidence, strengths and limitations of individual studies were evaluated based on scientific considerations detailed in the Appendix. More details on the causal framework used to reach these conclusions are included in the Preamble to the ISA (U.S. EPA, 2015). The evidence presented throughout this chapter support the following causality conclusions:

Size Fraction	Causality Determination
<i>Short-Term Exposure</i>	
PM _{2.5}	Causal
PM _{10-2.5}	Suggestive of, but not sufficient to infer
UFP	Suggestive of, but not sufficient to infer
<i>Long-Term Exposure</i>	
PM _{2.5}	Causal
PM _{10-2.5}	Suggestive of, but not sufficient to infer
UFP	Inadequate

6.1 Short-Term PM_{2.5} Exposure and Cardiovascular Effects

The 2009 PM ISA concluded that “a causal relationship exists between short-term exposure to PM_{2.5} and cardiovascular effects.” This conclusion was based on multiple lines of evidence including consistently positive associations between short-term exposure to PM_{2.5} and emergency department (ED) visits and hospital admissions for cardiovascular disease (U.S. EPA, 2009). Results from HA and ED visit studies were supported by associations between PM_{2.5} and cardiovascular mortality. In addition, controlled human exposure (CHE) and animal toxicological studies provided evidence of changes in various measures of cardiovascular function to establish biological plausibility for the epidemiologic findings. The most consistent PM_{2.5} effect was for reduced vascular function. Toxicological studies finding reduced myocardial blood flow during ischemia and altered vascular reactivity provided coherence and biological plausibility for the myocardial ischemia that was observed in both controlled

human exposure and epidemiologic studies. Further, PM_{2.5} effects on ST segment depression—an electrocardiogram change that potentially indicates ischemia—were also observed.

Key uncertainties from the last review included inconsistent results across disciplines with respect to the relationship between short-term exposure to PM_{2.5} and changes in blood pressure, blood coagulation markers, and markers of systemic inflammation. In addition, uncertainties remained with respect to biological plausibility; that is, how inhalation exposure to PM_{2.5} could trigger molecular, cellular, and tissue responses that result in serious cardiovascular outcomes. For example, in the 2009 PM ISA (U.S. EPA, 2009), there was a growing body of evidence from CHE, animal toxicological, and epidemiologic studies demonstrating changes in markers of systemic oxidative stress following PM_{2.5} exposure. However, uncertainties remained as to the relationship between changes in markers of oxidative stress and more serious cardiovascular health outcomes.

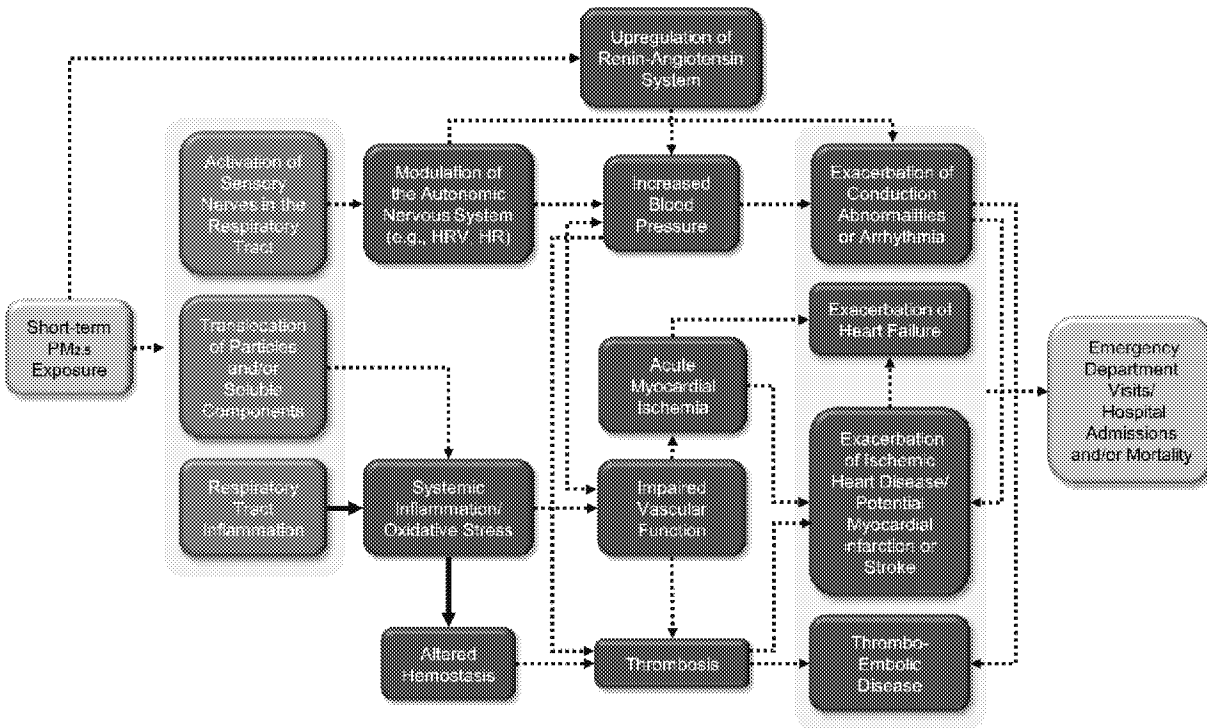
Since the last review, the evidence relating short-term PM_{2.5} CAP exposure and cardiovascular health effects has expanded greatly, further strengthening the conclusions reached in the 2009 PM ISA. Recent health evidence continues to show a clear relationship between short-term PM_{2.5} exposure and cardiovascular outcomes such as ED visits and hospital admissions for ischemic heart disease (IHD) and heart failure (HF). Additionally, recent epidemiologic studies confirm the relationship between short-term exposure to PM_{2.5} and cardiovascular mortality. Results from epidemiologic studies are supported by CHE and animal toxicological evidence demonstrating that exposure to PM_{2.5} can result in a variety of cardiovascular effects including endothelial dysfunction, increases in blood pressure, and conduction abnormalities. Thus, the epidemiologic, CHE and animal toxicological evidence presented in this section continues to support a causal relationship between short-term PM_{2.5} exposures and cardiovascular effects, with the strongest evidence supporting this determination still coming from the epidemiologic literature. As discussed in detail below, recent evidence also reduces uncertainties from the previous review with respect to the potential for copollutant confounding and provides additional evidence for biological plausibility.

The subsections below provide an evaluation of the most policy relevant scientific evidence relating short-term PM_{2.5} exposure to cardiovascular health effects. To clearly characterize and put this evidence into context, there is first a discussion of the biological plausibility of cardiovascular effects following short-term PM_{2.5} exposure (Section 6.1.1). Following this discussion, the health evidence relating short-term PM_{2.5} exposure and specific cardiovascular health outcomes is discussed in detail: ischemic heart disease and myocardial infarction (Section 6.1.2), heart failure and impaired heart function (Section 6.1.3) cardiac electrophysiology and arrhythmia (Section 6.1.4), cerebrovascular disease and stroke (Section 6.1.5), increased blood pressure and hypertension (Section 6.1.6), peripheral vascular disease (PVD), venous thromboembolism and pulmonary embolisms (Section 6.1.7), aggregated cardiovascular outcomes (Section 6.1.8), and cardiovascular-related mortality (Section 6.1.9). The evidence for an effect of PM_{2.5} exposures on endpoints such as changes in heart rate variability (HRV) and endothelial function are discussed (Section 6.1.10, Section 6.1.11, Section 6.1.12, and

1 Section 6.1.13), as are policy relevant considerations (Section 6.1.14), and the relationship between health
2 effects and exposure to specific PM_{2.5} components (Section 6.1.15). Finally, considering the all of the
3 information presented above, summary and causal determinations are presented (Section 6.1.16). Of note,
4 when discussing the health evidence and causal determinations, effect estimates from epidemiologic
5 studies adjusted for potential confounders are presented when available and new epidemiologic, CHE,
6 and animal toxicological studies that address uncertainties and limitations noted in the previous review
7 are emphasized.

6.1.1 Biological Plausibility

8 This subsection describes the biological pathways that potentially underlie cardiovascular health
9 effects resulting from short-term inhalation exposure to PM_{2.5}. Figure 6-1 graphically depicts these
10 proposed pathways as a continuum of pathophysiological responses—connected by arrows—that may
11 ultimately lead to the apical cardiovascular events observed in epidemiologic studies (e.g., ED visits and
12 hospital admissions). This discussion of "how" short-term exposure to PM_{2.5} may lead to these
13 cardiovascular events also provides biological plausibility for the epidemiologic results reported later in
14 Section 6.1. In addition, most studies cited in this subsection are discussed in greater detail throughout
15 Section 6.1.



Note: The boxes above represent the effects for which there is experimental or epidemiologic evidence, and the dotted arrows indicate a proposed relationship between those effects. Solid arrows denote direct evidence of the relationship as provided, for example, by an inhibitor of the pathway or a genetic knock-out model used in an experimental study. Progression of effects is depicted from left to right and color-coded (grey, exposure; green, initial event; blue, intermediate event; orange, apical event). Here, apical events generally reflect results of epidemiologic studies, which often observe effects at the population level. Epidemiologic evidence may also contribute to upstream boxes.

Figure 6-1 Potential biological pathways for cardiovascular effects following short-term exposure to PM_{2.5}.

When considering the available health evidence, plausible pathways connecting short-term exposure to PM_{2.5} to the apical events reported in epidemiologic studies are proposed in Figure 6-1. The first pathway begins as respiratory tract inflammation leading to systemic inflammation⁶¹. The second pathway involves activation of sensory nerve pathways in the respiratory tract that lead to modulation of the autonomic nervous system. Once these pathways are initiated, there is evidence from experimental and observational studies that short-term exposure to PM_{2.5} may result in a series of pathophysiological responses that could lead to cardiovascular events such as emergency department (ED) visits and hospital admissions for ischemic heart disease (IHD) and heart failure (HF), and ultimately mortality.

⁶¹ It is also possible that particles ~200 nm or less, or soluble particle components can translocate directly into the circulatory system (Chapter 4) and lead to systemic inflammation, although the extent to which particle translocation occurs remains unclear.

Short-term inhalation exposure to PM_{2.5} may result in respiratory tract inflammation and oxidative stress (CHAPTER 5). Inflammatory mediators such as cytokines produced in the respiratory tract have the potential to enter into the circulatory system where they may amplify the initial inflammatory response and/or cause distal pathophysiological events that can contribute to overt cardiovascular disease. For example, following short-term PM_{2.5} exposure in mice, [Budinger et al. \(2011\)](#) demonstrated that inflammation that began in the lung resulted in an increase in circulating markers of coagulation. Thus, it is important to note that there is evidence from CHE ([Behbod et al., 2013](#); [Urch et al., 2010](#); [Brook et al., 2009](#); [Gong et al., 2004](#)); epidemiologic panel ([Steenhof et al., 2014](#); [Strak et al., 2013a](#); [Huttunen et al., 2012](#); [Delfino et al., 2009b](#)), and animal toxicological ([Xu et al., 2013](#)) studies that short-term exposure to PM_{2.5} can result in an increase in circulating inflammatory cells and cytokines. Elevated levels of cytokines such as interleukin-6 (IL-6) have been correlated with elevated markers of thrombosis ([Chiarella et al., 2014](#); [Budinger et al., 2011](#)). It is therefore also important to note that in CHE ([Lucking et al., 2011](#); [Ghio et al., 2003](#); [Jr et al., 2000](#)), epidemiologic panel ([Croft et al., 2017](#); [Strak et al., 2013a](#)), and animal toxicological ([Budinger et al., 2011](#); [Kodavanti et al.](#)) studies that there is evidence of increased protein levels associated with coagulation and/or decreased protein levels associated with fibrinolysis following short-term PM_{2.5} exposure. This alteration in hemostasis increases the potential for thrombosis ([Lucking et al., 2011](#)), which can potentially exacerbate existing IHD and HF.

In addition to affecting hemostasis, systemic inflammation may result in impaired vascular function that could potentially lead to rupture of existing plaques ([Halvorsen et al., 2008](#)). Dislodged plaques may then obstruct blood flow to the heart or stimulate intravascular clotting ([Károly et al., 2007](#)), both of which could result in acute myocardial ischemia, and set the stage for HF. If the dislodged plaque obstructs blood flow to the brain, the potential for a stroke exists. Impaired vascular function has been reported following short-term PM_{2.5} exposure in CHE ([Hemmingsen et al., 2015b](#); [Tong et al., 2015](#); [Lucking et al., 2011](#); [Brook et al., 2009](#)), epidemiologic panel ([Ljungman et al., 2014](#); [Madrigano et al., 2010](#); [Liu et al., 2009](#)) and animal toxicological studies ([Davel et al., 2012](#); [Haberzettl et al., 2012](#); [O'Toole et al., 2010](#)). In addition, clinical indicators of potential ischemia (e.g., ST segment depression on an electrocardiogram) have been shown in epidemiologic panel studies ([Delfino et al., 2011](#); [Zhang et al., 2009](#)) following short-term exposure to PM_{2.5}. Impaired vascular function can also lead to increases in blood pressure (BP) through vasoconstriction. Given that increases in BP may exacerbate IHD or HF through shear stress induced arterial thrombosis and/or impaired vascular function, it is notable that following short-term PM_{2.5} exposure, there is direct evidence for increases in BP from CHE ([Tong et al., 2015](#); [Bellavia et al., 2013](#); [Brook et al., 2009](#)), epidemiologic panel ([Hicken et al., 2014](#); [Brook et al., 2011](#); [Dvonch et al., 2009](#)), and animal toxicological studies ([Bartoli et al., 2009](#); [Ito et al., 2008](#); [Chang et al., 2007](#); [Chang et al., 2004](#)). These studies are consistent with additional evidence from animal toxicological studies ([Aztatzi-Aguilar et al., 2015](#); [Ghelfi et al., 2010](#)) reporting increases in renin-angiotensin system gene expression consistent with vasoconstriction and increases in BP. Taken together, there are plausible pathways by which respiratory tract inflammation could exacerbate existing

IHD and HF, contribute to the development of a myocardial infarction or stroke, and lead to ED visits and hospital admissions.

There is also evidence that exposure to PM_{2.5} could lead to these outcomes through activation of sensory nerves in the respiratory tract (CHAPTER 5). Once activated, autonomic nervous system modulation may cause a shift toward increased sympathetic tone. Shifts toward increased sympathetic nervous system tone may result in increases in BP and decreased in vascular function, which as mentioned above, could exacerbate IHD and/or HF. It is therefore important to note that there is evidence from CHE (Tong et al., 2012); epidemiologic panel (Liu et al., 2015b; Hampel et al., 2014; Weichenthal et al., 2014a; Zanobetti et al., 2010) and animal toxicological studies (Wagner et al., 2014a; Wagner et al., 2014b; Rohr et al., 2011) of autonomic nervous system modulation—including a shift toward increased sympathetic tone (as evidenced by changes in HRV and/or HR)—following short-term PM_{2.5} exposure. Modulation of the autonomic nervous system may also contribute to conduction abnormalities (Ghelfi et al., 2010) or worsening of arrhythmia (Cascio, 2016). Thus, also of note is evidence from CHE (Tong et al., 2012; Sivagangabalan et al., 2011), epidemiologic panel (Zanobetti et al., 2014a; Link et al., 2013; Dockery et al., 2005a; Dockery et al., 2005b; Rich et al., 2005; Peters et al., 2000) and animal toxicological studies (Farraj et al., 2015; Ghelfi et al., 2010; Nadziejko et al., 2004) that short-term exposure to PM_{2.5} can result in conduction abnormalities or arrhythmia. Conduction abnormalities or arrhythmia could then potentially exacerbate IHD and subsequently, HF. Taken together, there are multiple potential pathways by which activation of sensory nerves in the respiratory tract may lead to worsening of IHD or HF.

When considering the available evidence, there are plausible pathways connecting short-term exposure to PM_{2.5} to cardiovascular health effects (Figure 6-1). The first potential pathway begins with respiratory tract inflammation that may lead to systemic inflammation, altered hemostasis, impaired vascular function and potential worsening of IHD and HF. The second potential pathway involves the activation of sensory nerves in the respiratory tract that may modulate autonomic nervous system responses potentially leading to exacerbation of IHD and HF through changes in BP and worsening of conduction abnormalities or arrhythmia. Collectively, these proposed pathways provide biological plausibility for epidemiologic results of ED visits and hospital admissions for cardiovascular-related causes and will be used to inform a causal determination, which is discussed later in the chapter (Section 0).

6.1.2 Ischemic Heart Disease and Myocardial Infarction

IHD is a chronic condition characterized by atherosclerosis and reduced blood flow to the heart (Section 6.2.2 and Section 6.2.4). Myocardial infarction (MI), more commonly known as a heart attack, occurs when heart tissue death occurs secondary to prolonged ischemia. The effect of short-term PM_{2.5} exposure on acute MI, complications from recent MI, and other acute or chronic IHD are generally